Title: An Open-Label, Phase 3 Trial to Investigate the Immunogenicity and Safety of Tetravalent Dengue Vaccine Candidate (TDV) at the End of Shelf Life in Healthy Adults in Non-Endemic Country(ies) for Dengue

NCT Number: NCT03771963

Protocol Approve Date: 21 June 2018

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**

An Open-Label, Phase 3 Trial to Investigate the Immunogenicity and Safety of Tetravalent Dengue Vaccine Candidate (TDV) at the End of Shelf Life in Healthy Adults in Non-Endemic Country(ies) for Dengue

**Immunogenicity and Safety of TDV at the End of Shelf Life in Healthy Adults**

| | |
|---|---|
| **Sponsor:** | Takeda Vaccines, Inc.<br>40 Landsdowne Street,<br>Cambridge, MA 02139<br>USA |
| **Trial Identifier:** | DEN-307 |
| **IND Number:** | 014292 **EudraCT Number:** Not Applicable |
| **Trial Vaccine Name(s):** | Takeda's 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). |
| **Takeda Approval Date:** | 21 June 2018 |
| **Version:** | Version 1.0 |

# 1.0 ADMINISTRATIVE INFORMATION

## 1.1 Contacts

| Issue | Contact |
|---|---|
| **Serious adverse event and pregnancy reporting** | PPD |

## 1.2 Approval

**REPRESENTATIVES OF TAKEDA**

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

- The ethical principles that have their origin in the Declaration of Helsinki [1].
- International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), E6 Good Clinical Practice: Consolidated Guideline [2].
- 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 (IB) , and any other product information provided by the sponsor. I agree to conduct this trial in accordance with the requirements of this protocol and 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 [1].
- International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), E6 Good Clinical Practice: Consolidated Guideline [2].
- 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 (SAEs) defined in Section 10.4.4 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 Version Summary of Changes

Not applicable

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## 2.0 TRIAL SUMMARY

| | | |
|---|---|---|
| **Name of Sponsor(s):**<br>**Takeda Vaccines, Inc.**<br>**40 Landsdowne Street, Cambridge, MA 02139, USA** | | **Product Name:**<br>**Takeda's Tetravalent Dengue Vaccine Candidate (TDV)** |
| **Trial Title:** An Open-Label, Phase 3 Trial to Investigate the Immunogenicity and Safety of Tetravalent Dengue Vaccine Candidate (TDV) at the End of Shelf Life in Healthy Adults in Non-Endemic Country(ies) for Dengue | | |
| **IND No.:** 014292 | **EudraCT No.:** Not applicable | |
| **Trial Identifier:** DEN-307 | **Phase:** 3 | **Blinding Schema:** Open-label |
| **Indication:** Prevention of dengue fever of any severity due to any serotype | | |

**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. An antiviral therapy for DENV infection is not 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 (Chimeric Yellow fever virus-Dengue virus Tetravalent Dengue Vaccine [CYD-TDV]) has been approved (in 2015) in some countries in Asia and Latin America. Initial findings showed that vaccine efficacy was different between serotypes and depended on dengue pre-exposure status. Additionally, recent analyses found that people who had not been infected by dengue virus before vaccination had a higher risk of getting severe disease when they were infected with dengue virus after vaccination with CYD-TDV. Hence, there is a continued unmet public health need for safer and more efficacious dengue vaccines.

**Takeda's 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 virus strain, originally isolated at Mahidol University, Bangkok, Thailand and generated by 53 serial passages in Primary Dog Kidney (PDK) cells (DENV-2 PDK-53). 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 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 chimeric strain (TDV-1), a dengue serotypes 2/3 chimeric strain (TDV-3), and a dengue serotypes 2/4 chimeric strain (TDV-4).

Nonclinical studies carried out in mice and nonhuman primates have demonstrated an acceptable safety, immunogenicity, and efficacy profile of TDV. Additionally, data from completed phase 1 and phase 2 clinical trials in humans have shown satisfactory reactogenicity, safety and immunogenicity profiles of TDV in healthy adults in non-endemic areas as well as in healthy adults and children in endemic areas in Asia and Latin America. Ongoing and completed phase 2 clinical trials have enabled the selection of a final TDV dose (lyophilized formulation) and a 2-dose vaccination regimen (2 single doses) 3 months (ie, 90 days) apart by subcutaneous (SC) injection for use in the ongoing pivotal program.

The current Investigator's Brochure contains additional product information and a more detailed review of nonclinical studies and clinical trials.

**Rationale for the Proposed Trial:**

The main purpose of this open-label phase 3 trial is to describe the immune response and safety of a naturally aged (>12 months stored at 2°C to 8°C) lot of TDV in a healthy adult population in country(ies) non-endemic for dengue. The assessment of a naturally aged lot of TDV in this clinical trial will provide an important contribution to data on TDV stability throughout the shelf life of the product.

A target of 200 subjects is planned to be enrolled in a single trial group. In all subjects, 2 doses of a naturally aged (>12 months stored at 2°C to 8°C) lot of TDV will be administered 3 months apart (ie, Day 1 [Month 0; M0] and Day 90 [M3]) and immunogenicity and safety will be assessed. The immunogenicity assessment for the primary endpoint is planned at 1 month post second dose (Day 120 [M4]) to coincide with the anticipated peak in post-vaccination antibody titers. As the trial will be conducted in country(ies) non-endemic for dengue, 6 months follow-up duration after the last dose is considered adequate.

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

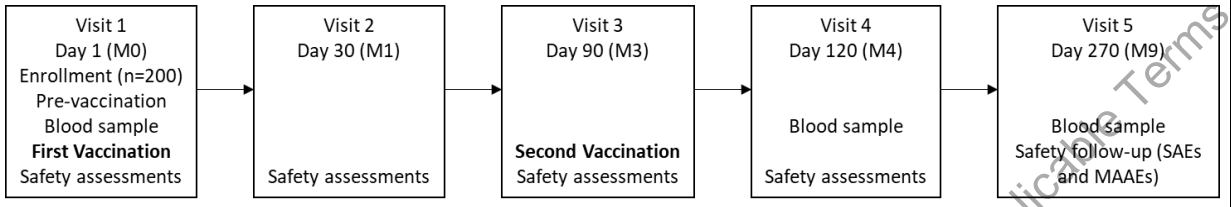
**Trial Design:**

This is an open-label phase 3 trial in country(ies) non-endemic for dengue to investigate the immunogenicity and safety of a lot of TDV with potency values representative of those at the end of shelf life, administered as a 2-dose regimen 3 months apart via SC injection. One single trial group of 200 healthy subjects aged 18 to 60 years, inclusive, will receive a naturally aged (>12 months stored at 2°C to 8°C) lot of TDV on Day 1 (M0) and Day 90 (M3).

All subjects will be followed-up for 6 months post second vaccination on Day 90 (M3) through Day 270 (M9), so the trial duration will be approximately 270 days (9 months) for each subject.

The schematic of the trial design is presented in Figure 2.a.

**Figure 2.a Schematic Trial Design**




M=Month; MAAEs=Medically Attended Adverse Events; SAEs= Serious Adverse Events.

**Immunogenicity evaluation:**

- Neutralizing antibodies will be measured (by Microneutralization Test 50% [$MNT_{50}$]) using blood samples collected pre first vaccination (Day 1 [M0]) and post second vaccination (Day 120 [M4] and Day 270 [M9]).

**Safety evaluation:**

- Diary cards will be distributed for the recording of solicited Adverse Events (AEs):
  - Solicited local (injection site) reactions for 7 days following each TDV dose on Day 1 (M0) and Day 90 (M3) (day of vaccination + 6 days). These will include: injection site pain, injection site erythema, and injection site swelling.
  - Solicited systemic events for 14 days following each TDV dose on Day 1 (M0) and Day 90 (M3) (day of vaccination + 13 days). These will include: fever, headache, asthenia, malaise, and myalgia.
- Unsolicited AEs for 28 days following each TDV dose on Day 1 (M0) and Day 90 (M3) (day of vaccination + 27 days) will be collected by interview and recorded for all subjects.
- Serious Adverse Events (SAEs), Medically Attended AEs (MAAEs) and AEs leading to subject discontinuation and withdrawal will be collected for the entire trial duration. MAAEs are defined as AEs leading to an unscheduled visit to or by a healthcare professional including visits to an emergency department, but not fulfilling seriousness criteria.

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

**Primary Objective:**

- To describe the neutralizing antibody response against each dengue serotype of a naturally aged (>12 months stored at 2°C to 8°C) lot of TDV at 1 month post second dose.

**Secondary Objectives:**

Immunogenicity

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

Safety

- To assess the safety profile following each vaccination.

**Subject Population:**

Healthy Subjects: Yes

Age Range: ≥18 and ≤60 years

Planned Number of Subjects: 200

Planned Number of Trial Arms: one TDV group; 2-dose regimen ( 1 TDV dose on Day 1 [M0] and 1 TDV dose on Day 90 [M3], SC route)

Estimated Total: 200 enrolled subjects

**Inclusion Criteria:**

1. The subject is aged ≥18 and ≤60 years.
2. Male or female.
3. Subjects 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.
4. The subject signs and dates a written informed consent 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.
5. Subjects who can comply with trial procedures and are available for the duration of follow-up.

**Exclusion Criteria:**

1. Subjects with a clinically significant active infection (as assessed by the investigator) or body temperature ≥38°C (≥100.4°F) within 3 days of the intended date of vaccine administration (consider whether applicable criterion for delay or as an exclusion criterion, see below).
2. Subjects with a known hypersensitivity or allergy to any of the trial vaccine components (including excipients).
3. Subjects 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. Subjects with any history of progressive or severe neurologic disorder, seizure disorder or neuro-inflammatory disease (eg, Guillain-Barré syndrome).
5. Subjects with any illness, or history of any illness that, in the opinion of the investigator, might interfere with the results of the trial or pose additional risk to the subjects 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 and/or ≥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 and/or ≥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. Known Human Immunodeficiency Virus (HIV) infection or HIV-related disease.
   g. Hepatitis C virus infection.
   h. Genetic immunodeficiency.
7. Abnormalities of splenic or thymic function.
8. Subjects with a known bleeding diathesis, or any condition that may be associated with a prolonged bleeding time.
9. Subjects with any serious chronic or progressive disease according to the judgment of the investigator (eg, neoplasm, hematologic malignancies, insulin dependent diabetes, cardiac, renal or hepatic disease).
10. Subjects with Body Mass Index (BMI) greater than or equal to 35 $kg/m^2$ (=weight in kg/height in $meters^2$).
11. Subjects participating in any clinical trial with another investigational product 30 days prior to Day 1 (M0) or intending to participate in another clinical trial at any time during the conduct of this trial.
12. Subjects who have received any other vaccines 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 after trial vaccine administration.
13. Subjects who have used antipyretics and/or analgesic medications within 24 hours prior to vaccination. The reason for their use (prophylaxis versus treatment) must be documented. Trial entry should be delayed to allow for a full 24 hours to have passed since last use of antipyretics and/or analgesic medications.
14. Subjects involved in the trial conduct or their first-degree relatives.
15. Subjects with history of substance or alcohol abuse within the past 2 years.
16. Female subjects who are pregnant or breastfeeding.

17. Subjects of childbearing potential[1] who are sexually active with men, and who have not used any of the acceptable contraceptive methods[2] for at least 2 months prior to Day 1 (M0).
18. Subjects of childbearing potential who are sexually active with men, and who refuse to use an "acceptable contraceptive method" [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.
19. Any positive or indeterminate pregnancy test.
20. Previous and planned vaccination (during the trial conduct), against any flavivirus including dengue, Yellow Fever (YF), Japanese Encephalitis (JE) viruses or tick-borne encephalitis.
21. 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.
22. Subjects with a current or previous infection with a flavivirus such as dengue, Zika, YF, JE, WN fever, tick-borne encephalitis or Murray Valley encephalitis and subjects with a history of prolonged (≥1 year) habitation in a dengue endemic area.
23. Planned travel (during trial conduct) to any endemic area for dengue and other flaviviruses.

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(s) or vaccine[s]). 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 trial vaccine administration at Day 90 (M3):

After enrollment, subjects may encounter clinical circumstances that warrant a delay in the administration of trial vaccine. These situations are listed below. In the event that a subject meets a criterion for delay of trial vaccine administration, the subject may receive the trial vaccine once the window for delay has passed as long as the subject is otherwise eligible for trial participation.

If any of the conditions below occur at the time scheduled for the trial vaccine administration at Day 90 (M3), the second dose may be administered at a later date as long as the subject is otherwise eligible to continue trial participation. In certain situations, the period of delay may lead to deviation from the time window for the second dose at Day 90 (M3). The decision to vaccinate in those situations will be made by the investigator.

The following clinical circumstances warrant a delay in the administration of trial vaccine at Day 90 (M3):

- Subjects with a clinically significant active infection (as assessed by the investigator) or body temperature ≥38.0°C (≥100.4°F) within 3 days of planned trial vaccine administration (consider at Day 1 [M0] whether applicable as an exclusion criterion, see above).
- Subjects who have received any other vaccines within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to planned trial vaccine administration.
- Known or suspected altered or impaired immune function as specified under the exclusion criteria.
- Subjects who have used antipyretics and/or analgesic medications within 24 hours prior to vaccination. The reason for their use (prophylaxis versus treatment) must be documented. Trial vaccine administration should

[1] Defined as status post onset of menarche and not meeting any of the following conditions: menopausal (at least 2 years previously), bilateral tubal ligation (at least 1 year previously), bilateral oophorectomy (at least 1 year previously) or hysterectomy.

[2] Hormonal contraceptives (eg, oral, injection, transdermal patch, implant, cervical ring), barrier method (condom with spermicide or diaphragm with spermicide) 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.

be delayed to allow for a full 24 hours to have passed between having used antipyretics and/or analgesic medications and trial vaccine administration.

Criteria for contraindication to trial vaccine administration at Day 90 (M3):

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

**Trial vaccine(s):**

The investigational vaccine is TDV, a tetravalent dengue vaccine comprised of 1 molecularly characterized, attenuated dengue virus strain (TDV-2), 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 sodium chloride solution) prior to administration. In this trial, a naturally aged lot of TDV will be used: material that was initially stored in the freezer (CCI and was then stored in the refrigerator (at 2°C to 8°C) for >12 months.

*Route of administration*

SC route

**Duration of the Trial and Subject Participation:**

The trial duration for each subject will be approximately 270 days (9 months).

**Criteria for Evaluation and Analyses:**

**Primary Endpoint:**

- Geometric Mean Titers (GMTs) of neutralizing antibodies (by $MNT_{50}$) for each of the 4 dengue serotypes at Day 120 (M4).

**Secondary Endpoints:**

*Immunogenicity*

- Seropositivity rates (% of seropositive subjects) for each of the 4 dengue serotypes at Day 120 (M4) and Day 270 (M9).
- Seropositivity rates (% of seropositive subjects) for each of the multiple (2, 3, or 4) dengue serotypes at Day 120 (M4) and Day 270 (M9).

  Note: Seropositivity is defined as a reciprocal neutralizing titer ≥10.
- GMTs of neutralizing antibodies (by $MNT_{50}$) for each of the 4 dengue serotypes at Day 270 (M9).

*Safety*

- Frequency and severity of solicited local (injection site) reactions for 7 days (day of vaccination + 6 days) and solicited systemic events for 14 days (day of vaccination + 13 days) after each TDV dose on Day 1 (M0) and Day 90 (M3).
- Percentage of subjects with any unsolicited AEs for 28 days (day of vaccination + 27 days) after each TDV dose on Day 1 (M0) and Day 90 (M3).
- Percentage of subjects with SAEs throughout the trial.
- Percentage of subjects with MAAEs 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 enrolled subjects who received at least 1 dose of trial vaccine and for whom a valid pre-dose (Baseline) measurement and at least one valid post-dose measurement is available for immunogenicity assessments.

**Per-protocol set (PPS):** The PPS will exclude all subjects seropositive for dengue virus at Baseline and will include all subjects in the FAS who have no major protocol violations. The categories of major protocol violations include: (1) not meeting selected entry criteria, (2) receiving prohibited therapies, (3) not receiving 2 doses of trial vaccine or receiving the second trial dose inadmissibly outside of the visit window, and (4) other major protocol violations that may be identified during 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.

Analysis of demographics and other baseline characteristics

Age, gender, race, and other baseline characteristics will be summarized descriptively for all enrolled subjects.

Immunogenicity analysis

For the primary and secondary immunogenicity endpoints (ie, GMTs of neutralizing antibodies and seropositivity rates for each of the 4 dengue serotypes and seropositivity rates for multiple dengue serotypes), descriptive statistics and 95% CIs will be provided for each applicable visit (Day 120 [M4] and Day 270 [M9]). Seropositivity is defined as a reciprocal neutralizing titer ≥10.

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

The handling of missing data will be described in the Statistical Analysis Plan.

Safety analysis

All safety data will be summarized using the safety set.

*Solicited AEs*

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

For each solicited AE, the number and percentage of subjects with local (injection site) reactions and systemic events will be summarized by event severity for each day after each vaccination (ie, Day 1 through Day 7 for local [injection site] reactions and Day 1 through Day 14 for systemic events), 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.

Persistent/prolonged solicited local reactions or systemic events continuing on Day 8 or Day 15, respectively, following each trial vaccination will be assessed separately. Unless otherwise specified these reactions/events will not be included in the analyses/tabulations of unsolicited AEs and will have separate listings.

*Unsolicited AEs*

Unsolicited AEs will be assessed for 28 days following each TDV dose (day of vaccination + 27 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).

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

AEs leading to subject discontinuation or vaccine withdrawal will be collected and summarized for the entire trial period.

*SAEs*

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

*MAAEs*

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

**Sample Size Justification:**

This trial is designed to be descriptive and is not based on testing formal null hypotheses. Therefore, the sample size was not determined based on formal statistical power calculations. The number of subjects is considered to be sufficient for the evaluation of the objectives of the trial.

**Interim Analysis:**

No interim analysis is planned for this trial.

**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-307 Version 1.0 (21 June 2018)**

## 2.1 Schedule of Trial Procedures

| **Visit** | **1** | **2 [a]** | **3** | **4 [a]** | **5** |
|---|---|---|---|---|---|
| **Day** | **Day 1 M0** | **Day 30 M1** | **Day 90 M3** | **Day 120 M4** | **Day 270 M9 (ET)[b]** |
| **Visit window (days)** | **1±NA** | **30 days (-1/+7) after Visit 1** | **90 days (-4/+7) after Visit 1** | **30 days (-1/+7) after Visit 3** | **180 days (-7/+14) after Visit 3** |
| Informed consent [c] | X | | | | |
| Assessment of eligibility criteria [d] | X | | | | |
| Demographics | X | | | | |
| Medical history | X | | | | |
| Prior and Concomitant medications/vaccinations [e] | X | X | X | X | X |
| Check contraindications to TDV administration | | | X | | |
| Check criteria for delay of TDV administration | | | X | | |
| Complete physical examination [f] | X | | X | | |
| Targeted physical examination [g] | | X | | X | X |
| Vital signs [h] | X | X | X | X | X |
| Pregnancy test [i] | X | | X | | |

| | | | | | | |
|---|---|---|---|---|---|---|
| Pregnancy avoidance guidance [j] | | X | X | X | X | |
| Blood sample for dengue neutralizing antibodies (5 mL) [k] | | X | | | X | X |
| TDV administration by SC injection | | X | | X | | |
| Injection site evaluation [l] | | X | | X | | |
| Diary card[m] | Distribution | X | | X | | |
| | Review/collection of solicited local (injection site) reactions and systemic events | | X | | X | |
| Unsolicited AEs [n] | | X | X | X | X | |
| SAEs, AEs leading to subject discontinuation or vaccine withdrawal, MAAEs [o] | | X | X | X | X | X |

AEs=Adverse Events, D=Day, ET=Early Termination, M=Month, MAAEs=Medically Attended Adverse Events, NA=Not Applicable, SAEs=Serious Adverse Events; SC= Subcutaneous; TDV=Tetravalent Dengue Vaccine Candidate.

(a) Visit 2 and Visit 4 should occur 30 days (at least 29 days) after the 1st and 2nd trial vaccination, respectively.
(b) The final visit will be made on Day 270 (Month [M]9). If the subject terminates early, Day 270 (M9) procedures should be performed at their last visit, if possible.
(c) Prior to the subject entering into the trial, and before any protocol-directed procedures are performed. Up to 28 days prior to the day of enrollment.
(d) Review of inclusion/exclusion criteria will be performed prior to Tetravalent Dengue Vaccine Candidate (TDV) administration on Day 1 (M0). After written informed consent has been obtained and eligibility is assessed, subjects will be enrolled to receive 2 doses of TDV by subcutaneous injection.
(e) All medications and vaccine history from 1 month (minimum 28 days) prior to administration of each trial dose of TDV 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). Concomitant medication/vaccination will be collected throughout the trial conduct.
(f) Physical examination including measurement of weight and height; Body Mass Index (BMI) will be calculated. Measurement of height is only required at Day 1 (M0).
(g) 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 "Adverse Event" Case Report Form (CRF).
(h) Vital signs including (but not limited to) the measurement of systolic blood pressure/diastolic blood pressure, heart rate, and body temperature.
(i) 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.
(j) Females of childbearing potential who are sexually active will be reminded during trial visits to adhere to acceptable contraceptive methods up to 6 weeks post second trial vaccination at Day 90 (M3). Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy and donation of ova. During the course of the trial, subjects of childbearing potential will receive continued guidance with respect to the avoidance of pregnancy.

(k) The blood sample on Day 1 (M0) should be taken prior to administration of Dose 1. The blood sample on Day 120 (M4) should be taken at least 29 days (-1, 7 days) after administration of Dose 2. At Day 270 (M9) a final blood sample will be taken.
(l) Injection site pain, erythema, and swelling assessed by trial staff for 30 minutes post-vaccination.
(m) Diary cards (paper or electronic) will be distributed for the collection of 1) solicited local (injection site) reactions for 7 days (day of vaccination + 6 subsequent days) following each trial vaccination, and 2) solicited systemic events for 14 days (day of vaccination + 13 subsequent days) following each trial vaccination. The investigator will categorize events by severity (mild, moderate or severe) and will assess causality of solicited systemic events to vaccine administration (related or not related).
(n) Unsolicited Adverse Events (AEs) for 28 days (day of vaccination + 27 subsequent days) following each trial vaccination will be collected by interview and recorded for all subjects at Day 30 (M1) and Day 120 (M4). The investigator will categorize events by severity (mild, moderate or severe) and will assess causality to trial vaccine administration (related or not related). If solicited local reactions or systemic events continue on Day 8 or Day 15, respectively, following each trial vaccination, record the end date of the event on the "Adverse Event" CRF.
(o) Serious AEs, AEs leading to subject discontinuation or vaccine withdrawal and Medically Attended AEs and will be collected for the trial duration.

# 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 vendors identified in the template for specific trial-related activities will perform these activities in full or in partnership with the sponsor.

## 3.2 Principal Investigator

The sponsor will select a Signatory Principal Investigator (PI) 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 PI 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(s) | Adverse Event(s) |
| BMI | Body Mass Index |
| CFR | Code of Federal Regulations |
| CRF | Case Report Form |
| CYD-TDV | Chimeric Yellow fever virus-Dengue virus Tetravalent Dengue Vaccine |
| 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 |
| FAS | Full Analysis Set |
| FDA | Food and Drug Administration |
| GCP | Good Clinical Practice |
| GMT(s) | Geometric Mean Titer(s) |
| HIV | Human Immunodeficiency Virus |
| IB | Investigator's Brochure |
| 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 |
| M0, 1, 3, 4, 9 | Month 0, 1, 3, 4, 9 |
| MAAE(s) | Medically Attended Adverse Event(s) |
| MedDRA | Medical Dictionary for Regulatory Activities |
| MHRA | The Medicines and Healthcare Products Regulatory Agency of United Kingdom |
| $MNT_{50}$ | Microneutralization Test 50% |
| PDK | Primary Dog Kidney |
| PI | Principal Investigator |
| PMDA | The Pharmaceuticals and Medical Devices Agency of Japan |
| PPS | Per-Protocol Set |
| prM | Pre-Membrane |
| PT | Preferred Term |
| SAE(s) | Serious Adverse Event(s) |
| SAP | Statistical Analysis Plan |
| SC | Subcutaneous |
| SOC | System Organ Class |

| | |
|---|---|
| SUSAR | Suspected Unexpected Serious Adverse Reaction |
| TDV | Takeda's 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 |
| US(A) | United States (of America) |
| 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 [3-6].

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) [5-8].

Treatment of dengue fever is based solely on signs and symptoms, with fluid replacement required for hemorrhagic or shock cases. An antiviral therapy for DENV infection is not 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 [3-9]. A first tetravalent dengue vaccine (Chimeric Yellow fever virus-Dengue virus Tetravalent Dengue Vaccine [CYD-TDV]) has been approved (in 2015) in some countries in Asia and Latin America [10]. Initial findings showed that vaccine efficacy was different between serotypes and depended on dengue pre-exposure status [11]. Additionally, recent analyses found that people who had not been infected by dengue virus before vaccination had a higher risk of getting severe disease when they were infected with dengue virus after vaccination with CYD-TDV [12]. Hence, there is a continued unmet public health need for safer and more efficacious dengue vaccines.

**Takeda's 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 virus strain, originally isolated at Mahidol University,

Bangkok, Thailand and generated by 53 serial passages in Primary Dog Kidney (PDK) cells (DENV-2 PDK-53) [13]. 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 DENV virus strains, DENV-1 16007, DENV-3 16562 or DENV-4 1036 virus, respectively [14]. 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).

Nonclinical studies carried out in mice and nonhuman primates have demonstrated an acceptable safety, immunogenicity, and efficacy profile of TDV. Additionally, data from completed phase 1 and phase 2 clinical trials in humans have shown satisfactory reactogenicity, safety and immunogenicity profiles of TDV in healthy adults in non-endemic areas as well as in healthy adults and children in endemic areas in Asia and Latin America. Ongoing and completed phase 2 clinical trials have enabled the selection of a final TDV dose (lyophilized formulation) and a 2-dose vaccination regimen (2 single doses) 3 months (ie, 90 days) apart by subcutaneous (SC) injection for use in the ongoing pivotal program.

The current Investigator's Brochure (IB) contains additional product information and a more detailed review of nonclinical studies and clinical trials.

## 4.2 Rationale for the Proposed Trial

The main purpose of this open-label phase 3 trial is to describe the immune response and safety of a naturally aged (>12 months stored at 2°C to 8°C) lot of TDV in a healthy adult population in country(ies) non-endemic for dengue. The assessment of a naturally aged lot of TDV in this clinical trial will provide an important contribution to data on TDV stability throughout the shelf life of the product.

A target of 200 subjects is planned to be enrolled in a single trial group. In all subjects, 2 doses of a naturally aged (>12 months stored at 2°C to 8°C) lot of TDV will be administered 3 months apart (ie, Day 1 [Month 0; M0] and Day 90 [M3]) and immunogenicity and safety will be assessed. The immunogenicity assessment for the primary endpoint is planned at 1 month post second dose (Day 120 [M4]) to coincide with the anticipated peak in post-vaccination antibody titers. As the trial will be conducted in country(ies) non-endemic for dengue, 6 months follow-up duration after the last dose is considered adequate.

The trial will be conducted in accordance with the protocol, International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH), Good Clinical Practice (GCP) Guidelines, and applicable regulatory requirements [2].

# 5.0 TRIAL OBJECTIVES AND ENDPOINTS

## 5.1 Objectives

### 5.1.1 Primary Objective

To describe the neutralizing antibody response against each dengue serotype of a naturally aged (>12 months stored at 2°C to 8°C) lot of TDV at 1 month post second dose.

### 5.1.2 Secondary Objectives

Immunogenicity

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

Safety

- To assess the safety profile following each vaccination.

## 5.2 Endpoints

### 5.2.1 Primary Endpoint

- Geometric Mean Titers (GMT) of neutralizing antibodies (by Microneutralization Test 50% [$MNT_{50}$]) for each of the 4 dengue serotypes at Day 120 (M4).

### 5.2.2 Secondary Endpoints

Immunogenicity

- Seropositivity rates (% of seropositive subjects) for each of the 4 dengue serotypes at Day 120 (M4) and Day 270 (M9).
- Seropositivity rates (% of seropositive subjects) for each of the multiple (2, 3, or 4) dengue serotypes at Day 120 (M4) and Day 270 (M9).

  Note: Seropositivity is defined as a reciprocal neutralizing titer ≥10.
- GMTs of neutralizing antibodies (by $MNT_{50}$) for each of the 4 dengue serotypes at Day 270 (M9).

Safety

- Frequency and severity of solicited local (injection site) reactions for 7 days (day of vaccination + 6 days) and solicited systemic events for 14 days (day of vaccination + 13 days) after each TDV dose on Day 1 (M0) and Day 90 (M3).

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

# 6.0 TRIAL DESIGN AND DESCRIPTION

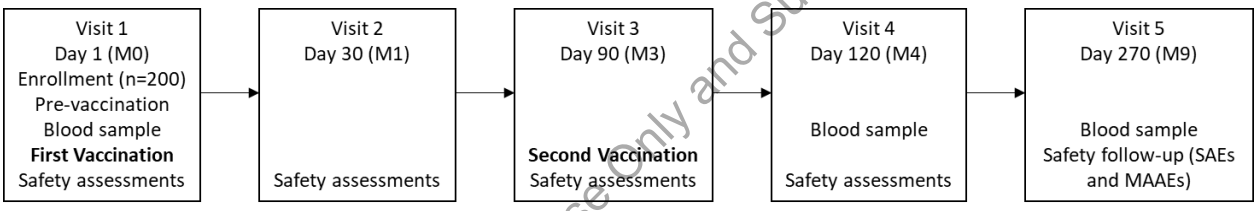
## 6.1 Trial Design

This is an open-label phase 3 trial in country(ies) non-endemic for dengue to investigate the immunogenicity and safety of a lot of TDV with potency values representative of those at the end of shelf life, administered as a 2 dose regimen 3 months apart via SC injection. One single trial group of 200 healthy subjects aged 18 to 60 years, inclusive, will receive a naturally aged (>12 months stored at 2°C to 8°C) lot of TDV on Day 1 (M0) and Day 90 (M3).

All subjects will be followed-up for 6 months post second vaccination on Day 90 (M3) through Day 270 (M9), so the trial duration will be approximately 270 days (9 months) for each subject.

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

**Figure 6.a Schematic of Trial Design**




M=Month; MAAEs=Medically Attended Adverse Events; SAEs= Serious Adverse Events.

Immunogenicity evaluation:

- Neutralizing antibodies will be measured (by $MNT_{50}$) using blood samples collected pre first vaccination (Day 1 [M0]) and post second vaccination (Day 120 [M4] and Day 270 [M9]).

Safety evaluation:

- Diary cards will be distributed for the recording of solicited AEs:
  - Solicited local (injection site) reactions for 7 days following each TDV dose on Day 1 (M0) and Day 90 (M3) (day of vaccination + 6 days). These will include: injection site pain, injection site erythema, and injection site swelling.
  - Solicited systemic events for 14 days following each TDV dose on Day 1 (M0) and Day 90 (M3) (day of vaccination + 13 days). These will include: fever, headache, asthenia, malaise, and myalgia.
- Unsolicited AEs for 28 days following each TDV dose on Day 1 (M0) and Day 90 (M3) (day of vaccination + 27 days) will be collected by interview and recorded for all subjects.
- SAEs, MAAEs and AEs leading to subject discontinuation and withdrawal will be collected for the entire trial duration. MAAEs are defined as AEs leading to an unscheduled visit to or by a healthcare professional including visits to an emergency department, but not fulfilling seriousness criteria.

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

## 6.2 Justification for Trial Design, Dose, and Endpoints

The trial design and the collection of solicited AEs, unsolicited AEs (serious and non-serious), and MAAEs following trial vaccine 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 Takeda's pivotal dengue 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.

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

Details related to the sample size are presented in Section 13.3.

The rationale for the proposed trial is given in Section 4.2. There is no interim analysis planned for this trial.

## 6.3 Planned 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 that require temporary suspension or early termination of the trial are satisfied.

- 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.
- The sponsor decides to terminate or suspend the trial.

### 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 enrollment.

## 7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria:

1. The subject is aged ≥18 and ≤60 years.
2. Male or female.
3. Subjects 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.
4. The subject signs and dates a written informed consent 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.
5. Subjects 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. Subjects with a clinically significant active infection (as assessed by the investigator) or body temperature ≥38°C (≥100.4°F) within 3 days of the intended date of vaccine administration (consider whether applicable criterion for delay or as an exclusion criterion, see Section 7.3).
2. Subjects with a known hypersensitivity or allergy to any of the trial vaccine components (including excipients).
3. Subjects 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. Subjects with any history of progressive or severe neurologic disorder, seizure disorder or neuro-inflammatory disease (eg, Guillain-Barré syndrome).
5. Subjects with any illness, or history of any illness that, in the opinion of the investigator, might interfere with the results of the trial or pose additional risk to the subjects 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 and/or ≥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 and/or ≥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) Known Human Immunodeficiency Virus (HIV) infection or HIV-related disease.

g) Hepatitis C virus infection.

h) Genetic immunodeficiency.

7. Abnormalities of splenic or thymic function.
8. Subjects with a known bleeding diathesis, or any condition that may be associated with a prolonged bleeding time.
9. Subjects with any serious chronic or progressive disease according to the judgment of the investigator (eg, neoplasm, hematologic malignancies, insulin dependent diabetes, cardiac, renal or hepatic disease).
10. Subjects with Body Mass Index (BMI) greater than or equal to 35 $kg/m^2$ (=weight in kg/height in $meters^2$).
11. Subjects participating in any clinical trial with another investigational product 30 days prior to Day 1 (M0) or intending to participate in another clinical trial at any time during the conduct of this trial.
12. Subjects who have received any other vaccines 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 after trial vaccine administration.
13. Subjects who have used antipyretics and/or analgesic medications within 24 hours prior to vaccination. The reason for their use (prophylaxis versus treatment) must be documented. Trial entry should be delayed to allow for a full 24-hours to have passed since last use of antipyretics and/or analgesic medications.
14. Subjects involved in the trial conduct or their first-degree relatives.
15. Subjects with history of substance or alcohol abuse within the past 2 years.
16. Female subjects who are pregnant or breastfeeding.
17. Subjects of childbearing potential who are sexually active with men and 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: menopausal for at least 2 years, status after bilateral tubal ligation for at least 1 year, status after bilateral oophorectomy for at least a year, or status after 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) 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.

18. Subjects of childbearing potential who are sexually active with men, and who refuse to use an "acceptable contraceptive method" (see exclusion number 17b) 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 (see Section 9.1.9).
19. Any positive or indeterminate pregnancy test (see Section 9.1.10).
20. Previous and planned vaccination (during the trial conduct), against any flavivirus including dengue, Yellow Fever (YF), Japanese Encephalitis (JE) viruses or tick-borne encephalitis.
21. 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.
22. Subjects with a current or previous infection with a flavivirus such as dengue, Zika, YF, JE, WN fever, tick-borne encephalitis or Murray Valley encephalitis and subjects with a history of prolonged (≥1 year) habitation in a dengue endemic area.
23. Planned travel (during trial conduct) to any endemic area for dengue and other flaviviruses.

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[s] or vaccine[s]). 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 Trial Vaccine Administration at Day 90 (M3)

After enrollment, subjects may encounter clinical circumstances that warrant a delay in the administration of trial vaccine. These situations are listed below. In the event that a subject meets a criterion for delay of trial vaccine administration, the subject may receive the trial vaccine once the window for delay has passed as long as the subject is otherwise eligible for trial participation. If any of the conditions below occur at the time scheduled for the trial vaccine administration at Day 90 (M3), the second dose may be administered at a later date as long as the subject is

otherwise eligible to continue trial participation. In certain situations, the period of delay may lead to deviation from the time window for the second dose at Day 90 (M3). The decision to vaccinate in those situations will be made by the investigator.

The following clinical circumstances warrant a delay in the administration of trial vaccine at Day 90 (M3):

- Subjects with a clinically significant active infection (as assessed by the investigator) or body temperature ≥38.0°C (≥100.4°F) within 3 days of planned trial vaccine administration (consider at Day 1 [M0] whether applicable as an exclusion criterion, see Section 7.2).
- Subjects who received any other vaccines within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to planned trial vaccine administration.
- Known or suspected altered or impaired immune function as specified under the exclusion criteria (see Section 7.2).
- Subjects who have used antipyretics and/or analgesic medications within 24 hours prior to vaccination. The reason for their use (prophylaxis versus treatment) must be documented. Trial vaccine administration should be delayed to allow for a full 24 hours to have passed between having used antipyretics and/or analgesic medications and trial vaccine administration.

### 7.4 Criteria for Early Termination of a Subject's Trial Participation

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 of trial participation. The primary reason for early termination of the subject's trial participation should be documented using the following categories. While the subject has no obligation to provide a reason for withdrawing consent, attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be documented.

For screen failure subjects, refer to Section 9.1.11.

1. Adverse Event: The subject has experienced an AE (irrespective of being related/unrelated to the trial vaccine(s), 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 of trial participation in this case will be 'withdrawal due to AE' and not 'withdrawal of consent', see below. Any ongoing AEs leading to early termination of trial participation should be followed up 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 were unsuccessful.

3. Withdrawal of consent: The subject 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 CRF.
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. Other. The specific reason should be recorded in the "specify" field of the CRF.

## 7.5 Criteria for Premature Discontinuation of Trial Vaccine Administration

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

Early termination of a subject's trial participation will by default prevent the subject from receiving further doses of trial vaccine, as the subject will no longer be participating in the trial. In addition to criteria for early termination of a subject's participation (see Section 7.4), other situations may apply in which subjects may continue participating in the trial (eg, contributing safety data according to protocol) but trial vaccine administration is discontinued. Even if the subject is deemed ineligible to receive further doses of 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 CRF ("End of Trial Vaccine Administration" CRF 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 administration(s) impose an unacceptable risk to the subject's health, but the subject will 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 three attempts to contact the subject were unsuccessful.
3. Withdrawal of consent: The subject 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 CRF.

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. 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. Other. The specific reason should be recorded in the "specify" field of the CRF.

# 8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

This section contains information regarding all trial 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 Vaccine(s) and Materials

The investigational vaccine is TDV, a tetravalent dengue vaccine comprised of 1 molecularly characterized, attenuated dengue virus strain (TDV-2), 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 sodium chloride solution) prior to administration.

In this trial, a naturally aged lot of TDV will be used: material was initially stored in the freezer CCI and was then stored in the refrigerator (at 2°C to 8°C) for >12 months.

### 8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

TDV kits (TDV and TDV diluent)
CCI

Lyophilized TDV is presented in a single-dose CCI

TDV diluent (37 mM NaCl solution) is a clear, colorless solution provided in a single-use CCI

TDV and TDV diluent are packaged together into single dose dispensing cartons. The units will be labeled to contain pertinent trial information in local languages. The sponsor will supply study sites with packaged and labeled TDV and TDV diluent. Further details can be found in the pharmacy manual.

### 8.1.2 Storage

TDV and TDV diluent will be shipped in refrigerated containers at CCI From receipt and prior to use, TDV and TDV diluent must be protected from light and stored at CCI in a refrigerator, do not freeze.

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 trial 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

TDV doses that will be provided to the single trial group are presented in Table 8.a:

The 0.5 mL TDV doses will be prepared and administered by the pharmacist or vaccine administrator according to the instructions in the pharmacy manual or per sponsor instructions.

The TDV doses will be administered by the SC route.

**Table 8.a Sponsor-Supplied Trial Vaccine**

| Group | Dose | Route | Number of subjects | Timing | |
|---|---|---|---|---|---|
| | | | | **Dose 1** | **Dose 2** |
| 1 | TDV | SC | 200 | Day 1 (M0) | Day 90 (M3) |

TDV=Tetravalent Dengue Vaccine Candidate, SC=Subcutaneous, M=Month.

## 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 vaccine.

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

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 personnel who are qualified to perform that function under applicable laws and regulations for that specific trial.

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

### 8.2.1 Precautions to be Observed when Administering the Trial Vaccine

Prior to trial vaccine administration, a subject must be determined to be eligible to receive trial vaccine and it must be clinically appropriate in the judgment of the investigator to administer the trial vaccine.

First, trial eligibility is evaluated according to the entry criteria outlined in this protocol (Sections 7.1, 7.2). Once eligibility is confirmed, the subject is able to receive the first trial vaccination.

Prior to subsequent trial vaccine administration, site staff must determine if the subject is eligible to receive vaccination by evaluating the criteria outlined in Section 7.3, 7.4, 7.5.

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 [15]. Before administering the trial vaccine, the vaccination site must be disinfected with a skin disinfectant (eg, 70% alcohol). Allow the skin to dry. Refer to the pharmacy manual for details on preparation and administration of trial vaccine.

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. These rescue medications will not be supplied by the sponsor.

### 8.3 Randomization Code Creation and Storage

Not applicable.

### 8.4 Trial Vaccine Blind Maintenance

Not applicable.

### 8.5 Unblinding Procedure

Not applicable.

### 8.6 Accountability and Destruction of Sponsor-Supplied Trial Vaccine(s), and other Clinical Trial Materials

Vaccine supplies will be counted and reconciled at the site before being destroyed locally or returned to the sponsor or designee as noted below. Sites will maintain source documents in addition to entering data in IRT. Other ancillary clinical trial materials will not be returned to the sponsor.

The investigator or designee must ensure that the sponsor-supplied trial vaccine(s) (including TDV diluent) are used in accordance with the approved protocol and is/are administered only to subjects enrolled in the trial. To document appropriate use of sponsor-supplied trial vaccine(s), the investigator must maintain records of all sponsor-supplied trial vaccine(s) (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 trial vaccine(s), the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, the trial vaccine is received within the labeled storage conditions (ie, no cold chain break has occurred during transit), and is in good condition. If quantity and conditions are acceptable, investigator or designee will acknowledge receipt of the shipment by recording in 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 Pharmacy Investigator Site File.

The investigator or designee must maintain 100% accountability for all sponsor-supplied trial vaccine(s) and other clinical trial material (including diluent) received and administered during their entire participation in the trial. Accountability includes, but is not limited to:

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

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

The investigator or designee must record the current inventory of all sponsor-supplied trial vaccine(s) (including diluent) on a sponsor-approved trial 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 trial vaccine(s), expiry 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 trial vaccine is administered.

Prior to site closure or at appropriate intervals throughout the trial, before any trial vaccine(s) are destroyed locally or returned to the sponsor or designee for destruction, a representative from the sponsor 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.

# 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. All procedures must be performed by qualified and trained staff.

### 9.1.1 Informed Consent Form

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

Informed consent must be obtained prior to the subject entering into the trial (up to 28 days prior to first administration of the trial vaccine), and before any protocol-directed procedures are performed.

A unique subject number will be assigned to each subject by the IRT after informed consent is obtained. 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 9.1.11).

### 9.1.2 Demographics, Medical History and Prior Medications

Demographic information to be obtained will include age/date of birth, sex, race and ethnicity as described by the subject.

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

Medical history (including corresponding medication) to be obtained will include any significant conditions or diseases that have disappeared or resolved at or prior to signing of informed consent.

Adverse medical occurrences emerging during the time between signing of informed consent form and the first administration of trial vaccine will be recorded in the "Medical History" CRF page. If such an adverse medical occurrence is assessed as related to a trial procedure this should be recorded in the CRF as an AE related to a trial procedure.

All 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), and concomitant medication/vaccination throughout the trial conduct are to be

collected as "Prior and Concomitant Medications" and recorded on the "Prior and Concomitant Medications" CRF page 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 documented in the subject's source documents and the CRF. 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 (Refer to Section 7.2):

- Parenteral immunoglobulin preparation, blood products, and/or blood-derived products within 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 within 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 within 30 days prior to Day 1 (M0).
- Use of antipyretics and/or analgesic medications within 24 hours prior to trial vaccine administration at Day 1 (M0) and/or Day 90 (M3). Trial vaccine administration should be delayed to allow for a full 24 hours to have passed since last use of antipyretics and/or analgesic medications.

These data must be written in the subject's source documents and CRF.

### 9.1.3 Documentation of Trial Entrance/Randomization

Randomization is not applicable for this trial. All subjects will be "enrolled" into a single trial group.

Only subjects who have a signed informed consent form, meet all of the inclusion criteria and none of the exclusion criteria are eligible for enrollment into the active phase.

If the subject is ineligible for enrollment, the investigator should record the primary reason for failure on the subject screening and enrollment log.

Any withdrawals or screen failures prior to vaccination at Day 1 (M0) will be replaced.

### 9.1.4 Physical Examination

Physical examinations must be performed by a qualified health professional in accordance with local regulations and as listed within the Site Responsibility Delegation Log. A complete physical examination will be performed on Day 1 (M0) and Day 90 (M3) according to the

investigator's standard practice. A complete physical examination includes but is not limited to: auscultation of heart and lungs, palpation of the abdomen, inspection of extremities (including skin over intended vaccination site[s]), and a check of general appearance and the measurement of weight and height. BMI will be calculated. Height will be only measured on Day 1 (M0).

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.

Targeted physical examination including but not limited to measurement of vital signs (see Section 9.1.5) will be performed at Day 30 (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 "Adverse Event" CRF.

Symptom-directed physical examination may be performed if deemed necessary.

### 9.1.5 Vital Signs

Vital signs will be measured on Day 1 (M0), Day 30 (M1), Day 90 (M3), Day 120 (M4), and Day 270 (M9). These will include (but are not limited to) the measurement of systolic blood pressure/diastolic blood pressure, heart rate, and body temperature.

### 9.1.6 Immunogenicity Assessments

Blood samples for measurements of dengue neutralizing antibodies (by $MNT_{50}$) will be collected from all subjects prior to the first TDV administration (on Day 1 [M0]), at 1 month after the second TDV administration (on Day 120 [M4]), and at 6 months after the second TDV administration (on Day 270 [M9]).

All samples must be collected in accordance with acceptable laboratory procedures.

### 9.1.7 Processing, Labeling and Storage of Biological Samples

All blood samples will be processed, labeled and stored according to the Laboratory Manual or other appropriate guideline provided to the site.

### 9.1.8 Safety Assessments

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

### 9.1.9 Contraception and Pregnancy Avoidance Procedure

For female subjects of childbearing potential, pregnancy testing 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 up to 6 weeks post second trial vaccination at Day 90 (M3). Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy and donation of ova. During the course of the trial, pregnancy tests will be performed only for women of childbearing potential and subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the trial procedures (Section 2.1). Refer also to Section 7.2.

### 9.1.10 Pregnancy

To ensure subject safety and the safety of the unborn child, each pregnancy in a subject having received 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 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 vaccine administration should be reported immediately, using a pregnancy notification form, to the contact listed in the Investigator Site File.

### 9.1.11 Documentation of Subjects who are not Randomized

Investigators must account for all subjects who sign an informed consent form. If the subject is found to be not eligible at this visit, the investigator should complete the CRF. Randomization is not applicable for this trial.

The primary reason for not receiving the trial vaccine is recorded in the CRF 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 the sponsor.
- Other (specify reason).

Subject numbers assigned to subjects who fail screening should not be re-used.

## 9.2 Monitoring Subject Compliance

The investigator or investigator's designee records all injections of trial vaccine (TDV) given to the subject in the subject's source document and the CRF.

## 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(s)/time point(s).

### 9.3.1 Pre-Vaccination Procedures (Day 1 [M0] and Day 90 [M3])

1. Before performing any trial procedure, the signed informed consent form needs to be obtained. Refer to Section 9.1.1.
2. Check inclusion and exclusion criteria. Refer to Sections 7.1 and 7.2.
3. Collect demographic data. Refer to Section 9.1.2.
4. Collect medical history, prior medications/vaccinations, and concomitant medications. Refer to Section 9.1.2.
5. Review of systems: Review of systems is a structured interview that questions the subject regarding any complaints they have experienced across each organ system.
6. Perform a complete physical examination. Refer to Section 9.1.4.
7. Check vital signs. Refer to Section 9.1.5.
8. Perform pregnancy testing (serum or urine) for female subjects of child bearing age. Refer to Section 9.1.10.
9. Provide female subjects of childbearing age with information on acceptable methods of contraception. Refer to Section 9.1.9.
10. Enrollment of the subject (Day 1 [M0]). Refer to Section 9.1.3.
11. Collect a pre-vaccination blood sample (Day 1 [M0]) from all subjects. 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. Confirm that the subject does not meet any criteria for delaying or cancelling additional trial vaccination (Day 90 [M3]); see Section 7.3, 7.4, 7.5.
2. Administer the vaccine. Refer to Section 8.1.3 and 8.2.

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

1. Careful training of the subject on how to measure solicited local (injection site) reactions 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 solicited local (injection site) reactions and those who will enter the information into the

diary card. This individual may or may not be the subject, but if a person other than the subject enters information into the diary card, this person's identity must be documented in the subject's source document and this person must receive training on the diary card. Training of the subject on how to measure an injection site reaction and how to take their temperature, as well as how to record the information in the diary card, should be performed while the subject is under observation after vaccination. Training of the subject should be documented in the subject's source document.

Diary card instructions must include the following:

- The individual(s) who will enter the information into the diary card must understand that timely completion of the diary card on a daily basis is a critical component of trial participation. This individual 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 individual(s) 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) reactions and systemic events (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.
- No corrections or additions to the diary card will be allowed after it is reviewed with the investigator/designee.
- Any data that is identified as implausible or incorrect, and confirmed by the subject to be a transcription error, should be corrected by the subject on the diary card (the correction should include a single strikethrough line and should be initialed and dated by the subject).
- Any blank or illegible fields on the diary card not otherwise corrected as above will be missing in the CRF.
- The site must enter all readable entries on the diary card into the CRF.
- Any newly described solicited safety information should be added to the diary card by the subject, initialed, and dated. Any new unsolicited safety information should be recorded in the subject source document as a verbally reported event and therefore captured as an AE and recorded in the "Adverse Event" CRF.
- Starting on the day of vaccination, the subject will check for specific types of events at the injection site (solicited local [injection site] reactions), any specific generalized symptoms (solicited systemic events), body temperature (any route may be used; the same route should be used consistently for temperature measurement), any other symptoms or change in the subject's health status, and any medications taken (excluding vitamins and minerals). These

solicited AEs (solicited local [injection site] reactions or solicited systemic events) and body temperature will be recorded in the diary. 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 should check their temperature. If the subject has fever, the highest body temperature observed that day should be recorded in the diary card.
- The measurements of solicited local (injection site) reactions (pain, erythema, and swelling) are to be performed using the ruler provided by the site.
- The collection on the diary card of solicited local (injection site) reactions, and solicited systemic events (including body temperature) will continue for a total of 7 days and 14 days respectively following each trial vaccine administration. Persistent/prolonged solicited local (injection site) reactions or systemic events continuing on Day 8 or Day 15 respectively, following each trial vaccination will be recorded in the subject source document as a verbally reported event and therefore captured as an AE and recorded in the "Adverse Event" CRF. Refer to Section 10.4.2.

2. Provide female subjects of childbearing age with pregnancy avoidance counseling. Refer to Section 9.1.9.
3. Collect and record unsolicited AEs. Refer to Section 10.4.1.
4. Collect and record MAAEs. Refer to Section 10.4.3.
5. Collect and record SAEs. Refer to Section 10.4.4.

After each trial vaccination, the subject will be observed for at least 30 minutes including observation for unsolicited AEs (non-serious and serious), solicited local (injection site) reactions, solicited systemic events, and body temperature measurement. Information should be recorded in the CRF. The investigator or delegate will take the opportunity to remind the subject how to measure solicited local (injection site) reactions 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.

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

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

Clinic visits that do not include a vaccination will be performed on Day 30 (M1), Day 120 (M4), and Day 270 (M9). These visits should occur at least 29 Days after the first and second vaccination on Day 1 (M0) and Day 90 (M3).

1. Interview the subject and check the diary card (Day 30 [M1], and Day 120 [M4]). Refer to Section 9.3.3.
2. Perform a targeted physical examination. Refer to Sections 9.1.4.
3. Check vital signs. Refer to Section 9.1.5.
4. Provide female subjects of childbearing age with pregnancy avoidance counseling. Refer to Section 9.1.9.
5. Record persistent/prolonged solicited AEs (Day 30 [M1], and Day 120 [M4]). Refer to Sections 9.3.3 and 10.4.2.
6. Record unsolicited AEs (Day 30 [M1], and Day 120 [M4]). Refer to Section 10.4.1
7. Record and collect MAAEs and SAEs. Refer to Sections 10.4.3 and 10.4.4.
8. Collect a blood sample from all subjects (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 Manuals.

The site should schedule the next trial activity with the subject.

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

### 9.3.5 Phone Contacts – Reminder Calls

Not applicable.

### 9.3.6 Phone Contacts – Safety Call

Not applicable.

### 9.3.7 Final (End of Trial) Visit

The final (end of trial) visit will be performed on Day 270 (M9). If a subject terminates earlier, the final (end of trial) visit procedures should be performed at their last trial visit, if possible. For all subjects receiving trial vaccine, the investigator must complete the End of Trial CRF page.

### 9.3.8 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 that was contracted by the sponsor for this purpose for up to but not 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 be used to assess, improve or develop tests related to dengue or other disease(s) or the investigational vaccine(s) that will allow more reliable measurement of the response to the investigational 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 (eg, 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 will be measured/collected for 7 days (solicited local [injection site] reactions) and 14 days (solicited systemic events) following administration of each trial vaccine dose (including the day of administration) and will be recorded on the "Local and Systemic Reactions" CRF page as applicable and as listed in Table 10.a.

Any solicited local (injection site) reaction or systemic event observed as continuing on Day 8 or Day 15, respectively, following each trial vaccination will be recorded as an AE on the "Adverse Event" CRF for follow-up. For these persistent/prolonged solicited AEs the end date will be captured on the "Adverse Event" CRF to permit a separate analysis from the unsolicited AEs (see Section 10.4.2).

**Table 10.a Solicited Local (Injection Site) Reactions and Systemic Events**

| | |
|---|---|
| Local (injection site) reactions: | Pain |
| | Erythema |
| | Swelling |
| Systemic events: | Fever [(a)] |
| | Headache |
| | Asthenia |
| | Malaise |
| | Myalgia |

(a) Fever is defined as body temperature greater than or equal to 38°C (100.4°F) regardless of method taken [16].

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 |
| | 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 |
| | 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 [16].

### 10.1.3 Adverse Events of Special Interest

Not applicable.

### 10.1.4 Medically Attended Adverse Events

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

### 10.1.5 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

Relationship (causality) to the trial vaccine(s) will also be assessed by the investigator. The relationship of each AE to the trial vaccine(s), including solicited systemic events (solicited local [injection site] reactions are considered as related by default) 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 a 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 trial 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 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, 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 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.

Trial procedures:

- Adverse occurrences related to trial procedures after signing of informed consent form are considered as AEs and 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 autopsy report should be supplied, if possible. All findings must be reported on an "Adverse Event" CRF and on the SAE form*, if necessary (see Section 10.4.4). All findings in subjects experiencing AEs must also be documented in the subject's source documents. Any unsolicited AEs will be collected for 28 days (day of vaccination + 27 subsequent days) following each trial vaccination during site visits via interview. AEs leading to discontinuation (from the trial or from the vaccination regimen) are collected throughout the trial. Even if the subject is deemed ineligible to receive further doses of trial vaccine, all efforts should be made to continue the collection of safety data according to protocol.

The following information will be documented for each event:

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

**SAE reporting will be done by CRF. If the CRF system is unavailable, a paper sponsor SAE form/paper CRF should be completed and the event must be entered into the CRF once access is restored.*

### 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 subjects for 7 days (solicited local [injection site] reactions) and 14 days (solicited systemic events) following administration of each trial vaccine dose (including the day of administration) and will be recorded on the "Local and Systemic AEs" CRF, as applicable. These will be summarized in the final report under the category "solicited AEs" to differentiate them from unsolicited AEs. Any solicited local (injection site) reaction or systemic event observed as continuing on Day 8 or Day 15, respectively, following each trial vaccination will be additionally recorded as an AE on the "Adverse Event" CRF for follow-up. For these persistent/prolonged solicited AEs, the end date will be captured on the "Adverse Event" CRF to permit a separate analysis from the unsolicited AEs. Any solicited local (injection site) reaction or systemic event that resolves before 8 or 15 days, respectively, following each trial vaccination, but recurs at a later time (ie, after the AE had discontinued), should be recorded as an unsolicited AE on the "Adverse Event" CRF.

Any solicited AE that meets any of the following criteria must be entered as an AE on the "Adverse Event" CRF page.

- Solicited local (injection site) reactions or systemic events that lead the subject to withdraw from the trial.
- Solicited local (injection site) reactions or systemic events that lead to the subject being withdrawn from the trial by the investigator.
- Solicited local (injection site) reactions and systemic events that otherwise meet the definition of an SAE (see Section 10.1.5).

### 10.4.3 Collection and Reporting of Adverse Events of Special Interest/Medically Attended Adverse Events

AEs of Special Interest will not be collected for this trial.

MAAEs will be collected for the trial duration: occurring from the first vaccination at Day 1 (M0) up to 6 months post second dose at Day 90 (M3), and will be collected by interview at Day 30 (M1), Day 90 (M3), Day 120 (M4), and Day 270 (M9) and must be recorded as an AE on the "Adverse Event" CRF.

### 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(s) (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.
- Causality assessment.
- Protocol number.
- Subject identification number.
- Investigator's name.
- Name of trial vaccine.

The SAE form should be transmitted within 24 hours to for 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.

### 10.5.2 Serious Adverse Events

If information not available at the time of the first report becomes available later, the investigator should complete a follow-up SAE form or provide other written documentation immediately. Copies of any relevant data from the hospital notes (eg, laboratory tests, discharge summary, postmortem results) should be sent to the sponsor.

All SAEs should be followed up until resolution, 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, Investigational Review Boards or Independent 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 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 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 vaccine 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 also 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 is 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 Trial-Specific Committees

### 11.1.1 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 RECORD KEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, medical history, and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Drugs will be coded using the WHO Drug Dictionary.

### 12.1 Case Report Forms (Electronic)

Completed CRFs are required for each subject who provides a signed informed consent.

The sponsor or designee will supply investigative sites with access to CRFs. The sponsor will make arrangements to train appropriate site staff in the use of the CRF. These forms are used to transmit the information collected in the performance of this trial to the sponsor and regulatory authorities. CRFs 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 designee[s]) and will be answered by the site.

Corrections to CRFs 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 PI must review the CRFs for completeness and accuracy and must sign and date the appropriate CRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the CRFs.

CRFs will be reviewed for completeness and acceptability at the trial site during periodic visits by trial monitors. The sponsor or designee will be permitted to review the subject's medical and hospital records pertinent to the trial to ensure accuracy of the CRFs. The completed CRFs 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 Appendix A and those documents that include (but are not limited to) the trial-specific documents, the identification log of all participating subjects, medical records. Temporary media such as thermal sensitive paper should be copied and certified, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent forms), electronic copy of CRFs, including the audit trail, and detailed records of vaccine disposition to enable evaluations or audits from regulatory authorities, the sponsor or designee. 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 Study Site Agreement between the investigator and sponsor.

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

# 13.0 STATISTICAL METHODS

## 13.1 Statistical and Analytical Plans

A Statistical Analysis Plan (SAP) will be prepared and finalized prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all trial objectives.

A data review will be conducted prior to database lock. This review will assess the accuracy and completeness of the trial database, subject evaluability, and appropriateness of the planned statistical methods.

### 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 enrolled subjects who received at least 1 dose of trial vaccine and for whom a valid pre-dose (Baseline) measurement and at least one valid post-dose measurement is available for immunogenicity assessments.

**Per-protocol set (PPS)**: The PPS will exclude all subjects seropositive for dengue virus at Baseline and will include all subjects in the FAS who have no major protocol violations. The categories of major protocol violations include: (1) not meeting selected entry criteria, (2) receiving prohibited therapies, (3) not receiving 2 doses of trial vaccine or receiving the second trial dose inadmissibly outside of the visit window, and (4) other major protocol violations that may be identified during 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 descriptively for all enrolled subjects.

### 13.1.3 Immunogenicity Analysis

For the primary and secondary immunogenicity endpoints (ie, GMTs of neutralizing antibodies and seropositivity rates for each of the 4 dengue serotypes and seropositivity rates for multiple dengue serotypes), descriptive statistics and 95% CIs will be provided for each applicable visit (Day 120 [M4] and Day 270 [M9]). Seropositivity is defined as a reciprocal neutralizing titer ≥10.

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

The handling of missing data will be described in the SAP.

### 13.1.4 Safety Analysis

All safety data will be summarized using the safety set.

*Solicited AEs*

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

For each solicited AE, the number and percentage of subjects with local (injection site) reactions and systemic events will be summarized by event severity for each day after each vaccination (ie, Day 1 through Day 7 for local [injection site] reactions and Day 1 through Day 14 for systemic events), 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.

Persistent/prolonged solicited local reactions or systemic events continuing on Day 8 or Day 15, respectively, following each trial vaccination will be assessed separately. Unless otherwise specified these reactions/events will not be included in the analyses/tabulations of unsolicited AEs and will have separate listings.

*Unsolicited AEs*

Unsolicited AEs will be assessed for 28 days following each TDV dose (day of vaccination + 27 days).

In all subjects, unsolicited AEs will be coded using the MedDRA and summarized by System Organ Class (SOC) and Preferred Term (PT).

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

AEs leading to subject discontinuation or vaccine withdrawal will be collected and summarized for the entire trial period.

*SAEs*

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

*MAAEs*

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

## 13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned for this trial.

## 13.3 Determination of Sample Size

This trial is designed to be descriptive and is not based on testing formal null hypotheses. Therefore, the sample size was not determined based on formal statistical power calculations. The number of subjects is considered to be sufficient for the evaluation of 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 CRFs. Source documents are defined as original documents, data, and records. The investigator and institution guarantee access to source documents by the sponsor or designee (clinical research organization) and by the IRB or IEC.

All aspects of the trial and its documentation will be subject to review by the sponsor or designee, including but not limited to the Investigator Site File, trial vaccine records, subject medical records, informed consent form documentation, documentation of subject authorization to use personal health information (if separate from the informed consent forms), and review of CRFs 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 designee. 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 Medicines and Healthcare Products Regulatory Agency of the United Kingdom [MHRA], the Pharmaceuticals and Medical Devices Agency of Japan [PMDA]). 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 trial subjects according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki [1], and the ICH Harmonized Tripartite Guideline for GCP [2]. 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 Institutional Review Board and/or Independent Ethics Committee 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. Those US sites unwilling to provide names and titles of all members due to privacy and conflict of interest concerns should instead provide a Federal Wide Assurance Number or comparable number assigned by the Department of Health and Human Services.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the IB, a copy of the informed consent 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 form must be obtained and submitted to the sponsor or designee before commencement of the trial (ie, before shipment of the trial vaccine(s) or trial specific screening activity). The IRB or IEC approval must refer to the trial by exact protocol title, number, and version date; identify versions of other documents (eg, informed consent form) reviewed; and state the approval date. The sponsor will notify the site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from the competent authority to begin the trial. Until the site receives notification no protocol activities, including screening may occur.

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

Incentives should not be used to exert undue influence on subjects 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 as described in the Declaration of Helsinki [1] and the ICH Guidelines for GCP [2] and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for the purpose of conducting the trial. The informed consent form and the subject information sheet further explain the nature of the trial, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the subject and the fact that the subject is free to withdraw at any time without giving a reason and without prejudice to the subject's further medical care.

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

The informed consent form, subject authorization form (if applicable), and subject information sheet must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC.

The subject 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 determines he or she will participate in the trial, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, at the time of consent and prior to the subject entering into the trial. The subject 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 form and subject authorization (if applicable) at the time of consent and prior to the 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, subject authorization form (if applicable), and subject information sheet will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent form in the subject's medical record and CRF. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by the subject in the same manner as the original informed consent form. The date the revised consent was obtained should be recorded in the subject's medical record and CRF, and the subject should receive a copy of the revised informed consent form.

## 15.3 Subject Confidentiality

The sponsor and designee 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, representatives from any regulatory authority (eg, FDA, MHRA, PMDA), 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 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 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 (ie, subject name, address, and other identifier fields not collected on the subject's CRF).

## 15.4 Clinical Trial Registration, Publication and Disclosure Policy

### 15.4.1 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, as a minimum register all clinical trials conducted in subjects that it sponsors anywhere in the world, on publicly accessible websites such as ClinicalTrials.gov and EudraCT, according to local requirements, before trial initiation. The sponsor contact information, along with the investigator's city, country, and recruiting status will be registered and available for public viewing.

### 15.4.2 Clinical Trial Results Disclosure

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

Primary Completion of Trial corresponds to the date on which the final subject was examined or received an intervention for the purposes of final collection of data for the primary outcome, whether the clinical trial concluded according to the pre-specified protocol or was terminated.

### 15.4.3 Publication of Trial Results

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 authorship, order of authors and choice of journal will be proposed by the sponsor to the PIs, to be eventually agreed upon by all authors themselves. The data analysis center for this trial will provide the analyses needed for publication. Information regarding this trial will be posted on ClinicalTrials.gov and/or other registries according to the local requirements.

## 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 Study Site Agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

## 16.0 REFERENCES

1. World Medical Association Declaration of Helsinki: ethical principals for medical research involving human subjects. JAMA 2013;310(20):2191-4.
2. International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH harmonized guideline. Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice E6 (R2). http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E6/E6_R2__Step_4_2016_1109.pdf. [Accessed 5 June 2018].
3. Simmons CP, Farrar JJ, Nguyen VVC, Wills B. Dengue. N Engl J Med 2012;366(15):1423-32.
4. 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.
5. Guzman GM, Kouri G. Dengue: an update. Lancet Infect Dis 2002;2(1):33-42.
6. World Health Organization. Dengue and severe dengue. Fact Sheet. http://www.who.int/mediacentre/factsheets/fs117/en/ [Accessed 12 March 2018].
7. World Health Organization. Dengue hemorrhagic fever: diagnosis, treatment, prevention and control, 2nd Edition. Geneva: http://www.who.int/csr/resources/publications/dengue/Denguepublication/en/ [Accessed 12 March 2018].
8. World Health Organization. Dengue guidelines for diagnosis, treatment, prevention and control. http://www.who.int/tdr/publications/documents/dengue-diagnosis.pdf. [Accessed 12 March 2018].
9. Halstead S, Deen J. The future of dengue vaccines. Lancet 2002;360(9341):1243-5.
10. Sanofi Pasteur, 2011. http://www.dengue.info [Accessed 12 March 2018].
11. 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.
12. Sanofi Pasteur, 2017. http://mediaroom.sanofi.com/sanofi-updates-information-on-dengue-vaccine [Accessed 12 March 2018].
13. 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.
14. Huang CY, Butrapet S, Tsuchiya KR, Bhamarapravati N, Gubler DJ, Kinney RM. Dengue 2 PDK-53 virus as a chimeric carrier for tetravalent dengue vaccine development. J Virol 2003;77(21):11436-47.

15. World Health Organization. Reducing pain at the time of vaccination: WHO position paper-September 2015.Wkly Epidemiol Rec 2015;90(39):505-10.

16. 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 that 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 conforms to 21 Code of Federal Regulations (CFR) Part 56, ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the trial to the IRB/IEC, and issue a final report within 3 months of trial completion.
7. Ensure that requirements for informed consent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
8. Obtain valid informed consent from each subject who participates in the trial, and document the date of consent in the subject's medical chart. Valid informed consent form is the most current version approved by the IRB/IEC. Each informed consent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the trial. If an informed consent form does not include such a subject authorization, then the investigator must obtain a separate subject authorization form from each subject.
9. Prepare and maintain adequate case histories of all persons entered into the trial, including CRFs, 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 the 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 studies 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 the 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.

Signature Page for DEN-307 Original Protocol, Version 1.0, 21 June 2018

Title: An Open-Label, Phase 3 Trial to Investigate the Immunogenicity and Safety

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