Title: A Phase II, double-blind, controlled trial to assess the Safety and Immunogenicity of different schedules of Takeda's Tetravalent Dengue Vaccine Candidate (TDV) in healthy subjects aged between 2 and <18 years and living in dengue endemic countries in Asia and Latin America

NCT Number: NCT02302066

Protocol Approve Date: 21 July 2016

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

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

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

PROTOCOL

A Phase II, double-blind, controlled trial to assess the Safety and Immunogenicity of different schedules of Takeda's Tetravalent Dengue Vaccine Candidate (TDV) in healthy subjects aged between 2 and <18 years and living in dengue endemic countries in Asia and Latin America

Safety and Immunogenicity of different schedules of TDV in healthy subjects

Sponsor:	Takeda Vaccines, Inc One Takeda Parkway Deerfield, IL 60015 U.S.A.		
Trial Identifier:	DEN-204		
IND Number:	014292	**EudraCT Number:**	Not Applicable
Vaccine Name:	Takeda's Tetravalent Dengue Vaccine Candidate (TDV)		
Date:	21 July 2016		
Version:	Version 4.0		

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

Table 1.a Contact Information

Issue	Contact
Serious adverse event and pregnancy reporting	PPD
Medical Monitor (medical advice on protocol, compound)	
Responsible Medical Officer (carries overall responsibility for the conduct of the trial)	

1.2 Protocol Amendment #4 Summary of Changes

1.2.1 Amendment History

Date	Amendment Number	Amendment Type	Region
13 March 2014	Initial Protocol	Not applicable	Global
11 April 2014	1	Non-substantial	Global
30 June 2014	2	Non-substantial	Global
23 July 2015	3	Substantial	Global
21 July 2016	4	Non-substantial	Global

1.2.2 Summary of Changes

Amendment to Protocol Version 3.0 dated 23 July 2015
Rationale for the Amendment: The previous protocol amendment (Protocol Amendment number 3, 23 July 2015) documented an extension of the study to 48 months. Prior to that amendment the study duration was 18 months and a benefit vaccine was offered at the 'end of the trial' (ie, 18 months). With the extension of the study to 48 months, it is considered inappropriate to withhold the benefit vaccine until the end of the trial (48 months). This amendment therefore clarifies that the benefit vaccine will be given at least 18 months after the first protocol defined vaccination, rather than being offered at the end of the trial (48 months) to maintain the original commitment. Additionally, as there is now a licensed dengue vaccine, the background section has been updated and the recording of the receipt of any licensed dengue vaccine has been added to the clinic visits and safety phone calls. This amendment is considered to be non-substantial.

Section	Description of change
1.2.1	Addition of protocol amendment to Amendment History
2.0, 4.1	Update of the background section regarding the recent approval of a tetravalent dengue vaccine (CYD-TDV) in some countries in Asia and Latin America.
2.0, 4.2, 9.3.7	Clarification that a licensed vaccine will be offered to all subjects, irrespective of their full participation in this trial and at least 18 months after the first protocol defined vaccination rather than being offered at the end of the trial.
2.1, 9.3.4	Addition that during clinic visits after vaccination, the receipt of any dose of any licensed dengue vaccine should be recorded using the concomitant medication page of the eCRF.
2.1, 9.3.5	Addition that during safety phone calls, the receipt of any dose of any licensed dengue vaccine should be recorded.
9.1.2	Addition that the receipt of any dose of any licensed dengue vaccine should be recorded troughout the trial.
16.0	Additional literature references.

1.3 Approval

REPRESENTATIVES OF TAKEDA

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonization E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

PPD

INVESTIGATOR AGREEMENT

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

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonization, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2 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)

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2.0 TRIAL SUMMARY

Name of Sponsor(s): Takeda Vaccines, Inc		**Product Name:** Takeda's Tetravalent Dengue Vaccine Candidate (TDV)
Trial Title: A Phase II, double-blind, controlled trial to assess the Safety and Immunogenicity of different schedules of Takeda's Tetravalent Dengue Vaccine Candidate (TDV) in healthy subjects aged between 2 and <18 years and living in dengue endemic countries in Asia and Latin America		
IND No.: 014292		**EudraCT No.:**Not Applicable
Trial Identifier: DEN-204	**Phase:** II	**Trial Blinding Scheme:** double-blind

Background and Rationale:

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

Dengue fever is clinically defined as an acute febrile illness with two or more manifestations (headache, retro-orbital pain, myalgia, arthralgia, rash, hemorrhagic manifestations, or leucopenia) and occurrence at the same location and time as other confirmed cases of dengue fever. Shock may cause death within 12 to 24 hours. The most severe forms of dengue infection – DHF and dengue shock syndrome (DSS) – are life threatening. Primary infection with any one of the four DENV 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 three DEN serotypes and may lead to an increased risk of severe disease (DHF/DSS).

Treatment of dengue fever is based solely on symptoms and signs, with fluid replacement required for severe fever and hemorrhagic or shock cases. No antiviral therapy for dengue virus infection is available. Preventive measures that rely on mosquito control and individual protection, are of limited efficacy, complex to implement and questionable in terms of cost-effectiveness. There is a great unmet global public health need for a safe and effective vaccine that will protect against dengue infection, and thereby reduce the morbidity and mortality associated with dengue disease. A tetravalent dengue vaccine (CYD-TDV) has been recently approved in some countries in Asia and Latin America. However, the initial findings suggest an unfavorable risk-benefit profile for younger subjects with the approved vaccine. Vaccine efficacy was different between serotypes and depended on dengue baseline seropositivity status. Hence, there is a continued unmet public health need for safer and more efficacious dengue vaccines. Additional vaccines are also important to ensure sufficient supply globally.

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

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

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

Data from two Phase I trials and a Phase II trial show satisfactory reactogenicity, safety and immunogenicity of Takeda's TDV in adults living in non endemic areas as well as in adults and children living in dengue endemic areas in Asia and Latin America. The investigational vaccine (lyophilized CC formulations) used in the Phase I and Phase II,

which is a tetravalent dengue vaccine comprised of four recombinant, live attenuated dengue virus strains CCI TDV-1, TDV-2, TDV-3 and TDV-4, respectively, generated a predominant immune response against DENV-2 and a relatively low immune response to DENV-4. For this reason, we will reduce the dose of only TDV-2 CCI in order to better balance the immune response to the four serotypes. The TDV dose formulation will be CCI of TDV-1, TDV-2, TDV-3 and TDV-4, respectively, vaccination schedule (one dose of vaccine), and route of administration (subcutaneous [SC] route) CCI The current Investigator Brochure of Takeda's TDV contains additional product information and a more detailed review of pre-clinical and clinical studies.

Rationale for the Phase II Trial:

Data generated to date show that the major part of the immune response to Takeda's TDV occur after the first dose, with the second dose having only a limited effect on geometric mean titers. Although this observation could suggest that a single dose of TDV may be sufficient, data on the persistence of immune responses after a single dose are limited by the administration of a second dose at 3 months. This trial will therefore assess the immune responses for up to ***48*** months after a single dose. Additional groups of subjects will either receive a 2 dose schedule (Month 0 and Month 3) or a booster vaccination given at Month 12. These 3 groups will enable a descriptive comparison of the immune responses to Takeda's TDV given as either a 2 dose primary series or as 1 primary dose with and without a booster at Month 12.

The trial will be conducted in subjects aged 2 to <18 years, living in dengue endemic countries in order to support a large scale Phase III efficacy trial in a similar population. CCI A total of 600 subjects (groups 1 and 4: 100 subjects each; groups 2 and 3: 200 subjects each) is considered sufficient for immunogenicity assessments and is defined as the immunogenicity subset. In order to limit the number of subjects with repeated blood sampling, fewer subjects are randomized into the immunogenicity subset from group 1 (which acts as a 2 dose immunogenicity control for the groups receiving 1 dose with or without a booster) and from group 4 (which acts as a safety control for the groups receiving TDV). Fewer group 1 and group 4 subjects in the immunogenicity subset also prevents the defacto unblinding that would result from all 200 subjects in those groups being included in the subset. Subjects included in the immunogenicity subset will be randomly selected using the Interactive Web/Voice Response System (IWRS/IVRS). CCI

Enrollment into each of the 4 groups is unbalanced such that the groups receiving a schedule likely to be taken into the Phase III studies are over-represented.

In order to maintain the double-blind design, a placebo injection (Phosphate Buffered Saline [PBS]) will be used at the appropriate time points. Outside the context of this trial, a licensed vaccine will be offered to all subjects, irrespective of their full participation in this trial and at least 18 months after the first protocol defined vaccination to provide benefit to the participants. The choice of this vaccine will be discussed by the medical monitor with each investigator and will need to be approved by the appropriate ethics committee. This vaccine will be used according to the registered indication in the country(ies).

Safety will be assessed in all subjects throughout the trial. This will include the collection of serious adverse events (SAEs) and identification of febrile episodes of potential dengue etiology. Detailed reactogenicity as well as unsolicited adverse events (AEs) up to 28 days after each vaccination (including day of vaccination) will only be

assessed in subjects included in the immunogenicity subset.

The trial will be conducted in accordance with the protocol, ICH-GCP Guidelines, 21 CFR Part 56 & 50 and any other applicable regulatory requirements.

Trial Design:

- This is a Phase II, double-blind, controlled, randomized trial that will enroll 1,800 healthy children aged 2 to <18 years old into 1 of 4 treatment groups:
  - **Group 1 (TDV 2-dose)**: receiving a two-dose primary vaccination at Day 1 (M0) and Day 91 (M3) with the trial vaccine. These subjects will also receive a placebo injection at Day 365 (M12).
  - **Group 2 (TDV 1-dose)**: receiving a one-dose primary vaccination at Day 1 (M0) with the trial vaccine. These subjects will also receive a placebo injection at Day 91 (M3) and Day 365 (M12).
  - **Group 3 (TDV 1-dose with booster)**: receiving a one-dose primary vaccination at Day 1 (M0) and booster vaccination at Day 365 (M12) with the trial vaccine. These subjects will also receive a placebo injection at Day 91 (M3).
  - **Group 4 (Placebo Control)**: receiving injections of placebo at Day 1 (M0), Day 91 (M3), and at Day 365 (M12).

Subjects will be randomized to these groups in a 1:2:5:1 ratio as shown in Table 1. Randomization will be stratified by age group based on the age at the time of informed consent: (1) 2 to 5 years of age, inclusive, (2) 6 to 11 years of age, inclusive, and (3) 12 to <18 years of age CCI [redacted]).

Table 1 Number of subjects per group

Group	No. of subjects	No. of subjects in the immunogenicity subset
Group 1	200	100
Group 2	400	200
Group 3	1,000	200
Group 4	200	100
Total	1,800	600

- Safety evaluation will include documentation of SAEs and identification of febrile episodes of potential dengue etiology in all subjects for the trial duration. In addition, all subjects in the immunogenicity subset will be provided with a diary card and will be instructed to record:
  - Solicited local adverse events (AEs) for 7 days following vaccination (day of vaccination + 6 days). These will include:
    - infant/toddler/child < 6 years: injection site pain, injection site erythema and injection site swelling.
    - adult and child (≥ 6 years): injection site pain, injection site erythema and injection site swelling.
  - Solicited systemic AEs for 14 days following vaccination (day of vaccination + 13 days). These will include:
    - infant/toddler/child < 6 years: fever, irritability/fussiness, drowsiness and loss of appetite.
    - adult and child (≥ 6 years): asthenia, fever, headache, malaise, myalgia.
  - Unsolicited AEs for 28 days following vaccination (day of vaccination + 27 days).
- Any subject with febrile illness (defined as temperature ≥ 38°C on 2 consecutive days) will be asked to return to the site for dengue fever evaluation. A dengue infection will be considered virologically confirmed by either positive polymerase chain reaction (PCR) or NS1 enzyme-linked immunosorbent assay (ELISA). A blood sample

will be collected within ≤ 5 days after the onset of fever to perform virological confirmation of dengue (approximately 4 ml) and for haematology (white cell count [WCC] and differential, platelet cell count [PCT] and hematocrit [HCT]) and biochemistry (aspartate transamininase [AST] and alanine transaminase [ALT]) to assess the severity of infection. Haematology and biochemistry will be performed by local laboratories and the volume will depend on local laboratory needs (typically 5 ml or less).

- Blood samples for the measurement of neutralizing antibodies (immunogenicity) will be collected as shown in Table 1 from a randomly selected subset of 600 subjects (100 subjects in group 1 and group 4 and 200 subjects in group 2 and group 3) CCI [redacted] Samples for immunogenicity will be taken as shown in Table 2 prior to vaccination and at intervals of 1, 3, 6, 12, 13, 18, 24, 36, and 48 months following the first vaccination. CCI [redacted] The rationale and volume of blood samples are given in Table 3.

Table 2 Timing of vaccination and blood sampling for immunological testing

Month	M 0	M 1	M 3	M 6	M 12	M 13	M 18	*M 24*	*M 36*	*M 48*
Group 1	S V	S	S V	S	S V*	S	S	*S*	*S*	*S*
Group 2	S V	S	S V*	S	S V*	S	S	*S*	*S*	*S*
Group 3	S V	S	S V*	S	S V	S	S	*S*	*S*	*S*
Group 4	S V*	S	S V*	S	S V*	S	S	*S*	*S*	*S*

V = vaccination (TDV)
V* = vaccination (placebo)
S = blood sample for immunogenicity; CCI [redacted]

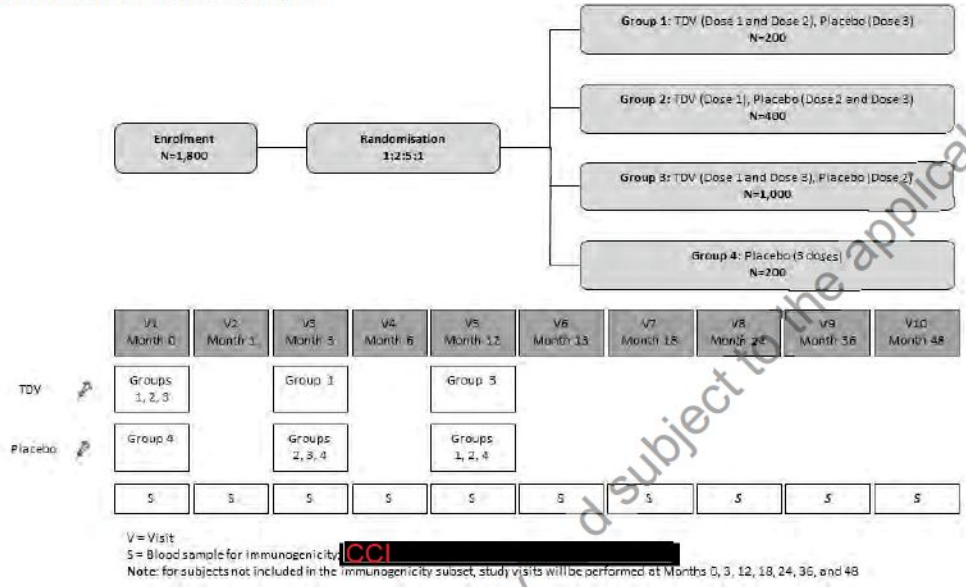
Table 3 Timing of vaccination and blood sampling for immunological testing

Population	Reason for blood sample	Approximate volume of blood	Number of visits in which blood is taken	Total volume of blood
Immunogenicity subset (600 subjects)	Measurement of neutralizing antibodies	4 ml	10	40 ml
CCI [redacted]				
All subjects with an acute febrile illness	Virological confirmation of dengue infection	4 ml	unscheduled	7 to 9 ml per febrile episode
	Clinical assessment of potential dengue infection	3 to 5 ml depending on local laboratory		

- For each subject, the duration of the trial will be 48 months and will include a total of 10 protocol-scheduled visits for subjects included in the immunogenicity subset and a total of 7 protocol-scheduled visits for subjects not included in the immunogenicity subset.
- Data collection: electronic Case Report Form (eCRF).

- Interim analyses on cleaned safety and immunogenicity data [CCI] are planned on data up to Month 6, and on data up to Month 18.

Figure 1 Schematic of Trial DEN-204



Primary Objective:

- To assess the humoral immune responses to subcutaneously administered TDV in a subset of healthy subjects aged between 2 and <18 years and living in dengue endemic countries.

Secondary Objectives:

Immunogenicity:

- To assess seropositivity rates following subcutaneously administered TDV in a subset of healthy subjects aged between 2 and <18 years and living in dengue endemic countries.

Safety:

- To evaluate the safety of subcutaneously administered TDV in healthy subjects aged between 2 and <18 years and living in dengue endemic countries.

Exploratory Objective:

- [CCI]

Criteria for Inclusion:

1. The subject is aged 2 to <18 years at the time of enrollment.
2. Individuals who are in good health at the time of entry into the trial as determined by medical history, physical examination (including vital signs), and clinical judgment of the investigator.
3. The subject or, when applicable, the subject's legally acceptable representative signs and dates a written, informed consent/informed assent form (and assent form where applicable) and any required privacy authorization prior to the initiation of any trial procedures, after the nature of the trial has been explained according to local regulatory requirements.
4. Individuals who can comply with trial procedures and are available for the duration of follow-up.

Criteria for Exclusion:

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

1. Febrile illness (temperature ≥ 38°C or 100.4°F) or moderate or severe acute illness or infection at the time of enrollment. Trial entry should be delayed until the illness has improved.
2. Individuals with history or any illness that, in the opinion of the investigator, might interfere with the results of the trial or pose additional risk to the subjects due to participation in the trial, including but not limited to:
    a. Known hypersensitivity or allergy to any of the vaccine components.
    b. Female subjects who are pregnant or breastfeeding.
    c. Individuals with any serious chronic or progressive disease according to judgment of the investigator (e.g. neoplasm, insulin dependent diabetes, cardiac, renal or hepatic disease, neurologic or seizure disorder or Guillain-Barré syndrome).
    d. Known or suspected impairment/alteration of immune function, including:
        i. Chronic use of oral steroids (Equivalent to 20 mg/day prednisone ≥ 12 weeks / ≥ 2 mg/kg body weight / day prednisone ≥ 2 weeks) within 60 days prior to Day 1 (use of inhaled, intranasal, or topical corticosteroids is allowed).
        ii. Receipt of parenteral steroids (Equivalent to 20 mg/day prednisone ≥ 12 weeks / ≥ 2 mg/kg body weight / day prednisone ≥ 2 weeks) within 60 days prior to Day 1.
        iii. Administration of immunoglobulins and/or any blood products within the three months preceding the first administration of the investigational vaccine or planned administration during the trial.
        iv. Receipt of immunostimulants within 60 days prior to Day 1.
        v. Immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy within 6 months preceding (first) vaccination.
        vi. HIV infection or HIV-related disease.
        vii. Genetic immunodeficiency.
3. Individuals who 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 of investigational vaccine administration.
4. Individuals participating in any clinical trial with another investigational product 30 days prior to first trial visit or intent to participate in another clinical trial at any time during the conduct of this trial.
5. Individuals who participated in a previous dengue vaccine trial .
6. Individuals who are first degree relatives of individuals involved in trial conduct.
7. If female of childbearing potential, sexually active, and has not used any of the "acceptable contraceptive methods" for at least 2 months prior to trial entry:
    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), bilateral tubal ligation (at least 1 year previously), bilateral oophorectomy (at least 1 year previously) or hysterectomy.
    b. Acceptable birth control methods are defined as one or more of the following:
        i. Hormonal contraceptive (such as oral, injection, transdermal patch, implant, cervical ring).
        ii. Barrier (condom with spermicide or diaphragm with spermicide) each and every time during intercourse.
        iii. Intrauterine device (IUD).

iv. Monogamous relationship with vasectomized partner. Partner must have been vasectomized for at least six months prior to the subjects' trial entry.

v. Sexual abstinence agreement

8. If female of childbearing potential, sexually active and refuses to use an "acceptable contraceptive method" through to 6 weeks after the last dose of investigational vaccine.

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

Investigational Vaccine(s):

- The Investigational Product is TDV, a tetravalent dengue vaccine comprised of four recombinant, live attenuated dengue virus strains CCI [redacted] of TDV-1, TDV-2, TDV-3 and TDV-4, respectively.
- The placebo vaccine is Phosphate Buffered Saline (PBS)

Duration of the Trial:	**Period of Evaluation:**
48 months for each participant	48 months after enrollment

Main Criteria for Evaluation and Analyses:

Primary Endpoint

- Geometric Mean Titers (GMTs) of neutralizing antibodies (microneutralization test [MNT_{50}]) for each of the four DENV serotypes at Months 1, 3, 6, 12, 13, 18, 24, 36, and 48.

Secondary Endpoints

Immunogenicity:

- Seropositivity rates (%) for each of the four DENV serotypes where seropositivity (MNT_{50}) is defined as a reciprocal neutralizing titer ≥ 10 at Months 1, 3, 6, 12, 13, 18, 24, 36, and 48.

Safety:

Immunogenicity subset:

- Frequency and severity of solicited local (injection site) AEs for 7 days and solicited systemic AEs for 14 days after each vaccination.
- Percentage of subjects with any unsolicited AEs for 28 days after each vaccination.

All Subjects:

- Percentage of subjects with SAEs throughout the trial.
- Percentage of subjects with virologically confirmed dengue throughout the trial.

Exploratory Endpoints:

CCI [redacted]

Statistical Considerations:

This trial is designed to assess the safety and immunogenicity of TDV when administered according to different vaccination schedules as defined above.

Analysis Sets

Safety Set: The Safety Set will consist of all randomized subjects who received at least one dose of the trial vaccine (including control vaccine). For analyses of solicited AEs and unsolicited non-serious AEs, only subjects in the immunogenicity subset will be included (600 subjects in total [groups 1 and 4: 100 subjects each; groups 2 and 3: 200 subjects each]). SAEs, virologically confirmed dengue and AEs leading to trial or vaccine withdrawal will be assessed for all subjects in the Safety Set.

Full Analysis Set (FAS): The Full Analysis Set will consist of all randomized subjects who received the trial vaccine (including control vaccine) and for whom valid pre-dosing and at least one valid post-dosing blood sample have been received.

Per-Protocol Set (PPS): The Per-Protocol Set will consist of all subjects in the FAS who have no major protocol violations. The major protocol violation criteria will be defined as part of the blinded data review prior to the unblinding of individual subject's treatment assignment. The categories of major protocol violations include: (1) not meeting selected entry criteria, (2) receiving wrong trial treatment, (3) receiving prohibited therapies, and (4) other major protocol violations that may be identified during blinded data reviews.

Both the FAS and PPS will include only subjects from the immunogenicity subset (600 subjects in total [groups 1 and 4: 100 subjects each; groups 2 and 3: 200 subjects each]), i.e., subjects for whom blood samples for assessment of dengue neutralizing antibodies are collected.

The primary analysis of immunogenicity will be based on the PPS, and other supportive analysis may be provided for the FAS. The safety analysis will be based on the Safety Set as described above.

Analysis of Demographics and Other Baseline Characteristics

Summaries of age, gender, and other baseline characteristics will be presented by treatment group.

Immunogenicity Analysis

The primary immunogenicity endpoint in the trial is Geometric Mean Titers (GMTs) of neutralizing antibodies (MNT_{50}) for each of the four DENV serotypes. The secondary endpoint is seropositivity rates (%) for each of the four DENV serotypes where seropositivity is defined as a reciprocal neutralizing titer ≥ 10 (MNT_{50}).

For the immunogenicity subset of subjects, descriptive statistics and 95% confidence intervals for both GMT and seropositivity will be computed by treatment group at Months 0, 1, 3, 6, 12, 13, 18, 24, 36, and 48. In addition, the percent of subjects with monovalent, bivalent, trivalent, and tetravalent seropositivity will be summarized by treatment group at each visit. Additional summaries of immunogenicity endpoints by baseline seropositivity status (positive or negative) will also be provided.

CCI [redacted]

Safety Analysis

All summaries of safety data are based on subjects in the Safety Set. Unless otherwise specified, the safety data will be summarized by treatment group.

Reactogenicity

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

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

Unsolicited Adverse Events

Unsolicited AEs and SAEs will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term (PT) for each treatment arm. AEs leading to trial or vaccine withdrawal will also be summarized.

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

The percentage of subjects with virologically confirmed dengue will also be summarized by treatment group.

Sample Size Justification:

This trial is designed to be primarily 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 will provide a reasonable sample size for the evaluation of the persistence of immune responses following administration of a single TDV dose, and of the effect of a TDV booster dose, and to provide an adequate safety database prior to initiating Phase III studies.

Interim Analysis: Interim analyses on cleaned safety and immunogenicity data CCI [redacted] are planned on data up to Month 6, and on data up to Month 18 to provide data to support the planning and execution of other studies in the development plan of Takeda's TDV. These interim analyses will be performed by a separate set of unblinded statisticians and programmers at the Clinical research organization (CRO). They will have access to individual treatment assignments but will not be involved in subsequent trial conduct. The rest of the personnel involved in the conduct of the trial, including those at Takeda, CRO, and the trial sites, will remain blinded to the individual subject data (including treatment assignments) until unblinding after trial completion (database lock for data through the Month 48 Follow Up visit). More details regarding the interim analyses will be provided in the statistical analysis plan.

2.1 Schedule of Trial Procedures

2.1.1 Schedule Trial Procedures for Immunogenicity Subset

Procedure	Vacc 1	Post Vacc 1	Vacc 2	Post Vacc 2	Vacc 3	Post Vacc 3	Follow-up	Follow-up	Follow-up	Follow-up/ET	Unscheduled
Visit	1	2	3	4	5	6	7	8	9	10	NA
Trial Timelines	D1 (M0)	D28 (M1)	D91[a] (M3)	D180 (M6)	D365 (M12)[b]	D393 (M13)[c]	D540 (M18)[d]	D730 (M24)[e]	D1095 (M36)[f]	D1460 (M48)[g]	
Time window		+5 days	± 15 days	± 15 days	± 15 days	+5 days	± 15 days	± 15 days	± 15 days	± 15 days	
Signed Informed Consent/Assent	X										
Medical History	X										
Demographics	X										
Assessment of eligibility criteria[i]	X										
Complete Physical Examination[j]	X										
Pregnancy Test[k]	X		X		X						
Brief symptom-directed physical assessment[l]		X	X	X	X	X	X	X	X	X	
Randomization	X										
Blood Sampling[h]	X	X	X	X	X	X	X	X	X	X	
Vaccine administration	X		X		X						
Injection site evaluation[m]	X		X		X						
Diary card[n] distribution	X[k]	X	X[k]		X[k]						
Diary card Collection and Review[o]		X[l]		X[l]		X[l]					
Safety Review Call[p]	X[m]										
Concomitant medication[q]	X	X	X	X	X	X	X	X	X	X	X
Febrile illness assessment											X
Blood sample febrile illness[r] (4 ml)											X

Note: The double-line border following Month 6 and Month 18 indicates the interim analyses which will be performed on cleaned safety and immunogenicity data[CCI]) up to Month 6 and up to Month 18, respectively; NA: not applicable; D: Day; M: Month; ET: Early termination; Vacc: vaccination

(a) 28 days Post Vacc 2, home visits may be done by the site staff in order to collect the diary card. Optionally, a phone call may be made to remind the subject to keep the diary card secure and bring to the site on the Month 6 visit.
(b) D1 + 364 days
(c) 28 days Post Vacc 3 (Day 365 + 28 days)
(d) D1 + 539 days
(e) D1 + 729 days
(f) D1 + 1094 days
(g) D1 + 1459 days
(h) Blood sampling before vaccination for immunogenicity CCI tests (Refer to Section 9.1.6).
(i) Review of inclusion/exclusion criteria will be documented before first vaccination.
(j) Physical examination at Day 1 (Refer to Section 9.1.4). Weight and height will also be measured and Body Mass Index (BMI) calculated. Includes Vital Signs.
(k) In women of childbearing potential, urine or serum pregnancy test will be performed before each vaccination (within one day prior).
(l) Including (but not limited to) the measurement of vital signs.
(m) At 30 minutes after vaccine administration.
(n) Diary cards will be distributed for the collection of
1) solicited local AEs occurring on the day of vaccination and the 6 subsequent days for a total of 7 days,
2) solicited systemic AEs occurring on the day of vaccination and the 13 subsequent days for a total of 14 days (Days 1 to 7 and Days 8 to 14), and
3) unsolicited AEs occurring on the day of vaccination and the 27 subsequent days for a total of 28 days.
(o) The investigator will categorize events by severity (mild, moderate or severe) and will assess causality to vaccine administration (related or not related).
(p) Monthly safety phone calls (M2, M4, M5, M7 to M11, M14 to M17, M19 to M23, M25 to M35, M37 to M47) when no study visit is scheduled. Safety phone calls (M2, M4, M5, M7 to M11, M14 to M17, M19 to M23, M25 to M35, M37 to M47) must be 30 days (-7/+14 days) after the last visit/call.
(q) Collected at clinic visits or phone contact, as applicable. Concomitant therapy and vaccine history from 4 weeks prior to administration of each dose of TDV or placebo, as applicable, and ending one month (minimum 28 days) after the last dose of TDV or placebo. Receipt of any dose of any licensed dengue vaccine throughout the trial.
(r) Blood sample to be collected from any subject with febrile illness (defined as temperature ≥ 38°C for 2 consecutive days).

2.1.2 Schedule Trial Procedures for Subjects Not Included in the Immunogenicity Subset

Procedure	Vacc 1	Vacc 2	Vacc 3	Follow-up[a]	Follow-up	Follow-up	Follow-up/ET	Unscheduled
Visit	1	2	3	4	5	6	7	NA
Trial Timelines	D1 (M0)	D91 (M3)	D365 (M12)[a]	D540 (M18)[b]	D730 (M24)[c]	D1095 (M36)[d]	D1460(M48)[e]	
Time window		± 15 days	± 15 days	± 15 days	± 15 days	± 15 days	± 15 days	
Signed Informed Consent/Assent	X							
Medical History	X							
Demographics	X							
Assessment of eligibility criteria[f]	X							
Complete Physical Examination[g]	X							
Pregnancy Test[h]	X	X	X					
Brief symptom-directed physical assessment[i]	X	X	X	X	X	X	X	
Randomization	X							
Vaccine administration	X	X	X					
Safety Review at the Site[j]		X	X	X				X
Safety Review Call[k]				X[h]				
Concomitant medication[l]	X	X	X	X	X	X	X	X
Febrile illness assessment								X
Blood sample febrile illness[m] (4 ml)								X

NA: not applicable; D: Day; M: Month; ET: Early termination; Vacc: vaccination

(a) D1 + 364 days
(b) D1 + 539 days
(c) D1 + 729 days
(d) D1 + 1094 days
(e) D1 + 1459 days
(f) Review of inclusion/exclusion criteria will be documented before first vaccination.
(g) Physical examination at Day 1 (Refer to Section 9.1.4). Weight and height will also be measured and Body Mass Index (BMI) calculated.
(h) In women of childbearing potential, urine or serum pregnancy test will be performed before each vaccination (within one day prior).
(i) Including (but not limited to) the measurement of vital signs.
(j) Review of SAEs/AEs (including Febrile Episodes) at Site. SAEs will be reported to the Sponsor within 24 hours of the investigator becoming aware of the event. The investigator will categorize events by severity (mild, moderate or severe) and will assess causality to vaccine administration (related or not related).
(k) Monthly safety phone calls (M1, M2, M4 to M11, M13 to M17, M19 to M23, M25 to M35, M37 to M47). Safety phone calls (M1, M2, M4 to M11, M13 to M17, M19 to M23, M25 to M35, M37 to M47) must be 30 days (-7/+14 days) after the last visit/call.
(l) Collected at clinic visits or monthly phone contact, as applicable. Concomitant therapy and vaccine history from 4 weeks prior to administration of each dose of TDV or placebo, as applicable, and ending one month (minimum 28 days) after the last dose

of TDV or placebo. Receipt of any dose of any licensed dengue vaccine throughout the trial.

(m) Blood sample to be collected from any subject with febrile illness (defined as fever ≥ 38°C for 2 consecutive days).

3.0 TRIAL REFERENCE INFORMATION

3.1 Trial-Related Responsibilities

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

3.2 Coordinating Investigator

The sponsor will select a Signatory Coordinating Investigator from the investigators who participate in the trial. Selection criteria for this investigator will include significant knowledge of the trial protocol, the investigational vaccine, their expertise in the therapeutic area and the conduct of clinical research as well as trial participation. The Signatory Coordinating Investigator will be required to review and sign the clinical trial report and by doing so agrees that it accurately describes the results of the trial.

3.3 List of Abbreviations

AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Transaminase
CCI	[redacted]
CRO	Clinical Research Organization
DEN	Dengue Virus
DENV	Dengue Vaccine Virus
DHF	Dengue Hemorrhagic Fever
DMC	Data Monitoring Committee
DSS	Dengue Shock Syndrome
eCRF	electronic Case Report Form
ELISA	Enzyme-Linked Immunosorbent Assay
FAS	Full Analysis Set
GMT	Geometric Mean Titer
GSD	Geometric Standard Deviation
hCG	Human Choriogonadotrophin Beta
HCT	Hematocrit
HLA	Human Leukocyte Antigen
IFN	Interferon
Il	Interleukin
IVRS	Interactive Voice Response System
IWRS	Interactive Web Response System
M(x)	Month (x)
MNT	Microneutralization Test
CCI	[redacted]
PBS	Phosphate Buffered Saline
PCC	Platelet Cell Count
PCR	Polymerase Chain Reaction
PFU	Plaque Forming Units
PPS	Per-Protocol Set
SAE	Serious Adverse Event
SC	Subcutaneous
SUSAR	Suspected Unexpected Serious Adverse Reaction

TDV	Takeda's Tetravalent Dengue Vaccine Candidate
TNF	Tumor Necrosis Factor
WCC	White Cell Count
WFI	Water For Injection

3.4 Corporate Identification

TVI	Takeda Vaccines, Inc
VBD	Vaccines Business Division

4.0 INTRODUCTION

4.1 Background

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

Dengue fever is clinically defined as an acute febrile illness with two or more manifestations (headache, retro-orbital pain, myalgia, arthralgia, rash, hemorrhagic manifestations, or leucopenia) and occurrence at the same location and time as other confirmed cases of dengue fever. Shock may cause death within 12 to 24 hours. The most severe forms of dengue infection – DHF and dengue shock syndrome (DSS) – are life threatening. Primary infection with any one of the four DENV 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 three DEN serotypes and may lead to an increased risk of severe disease (DHF/DSS) [4, 5, 6]. Primary infection with any one of the four DENV 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 three DENV serotypes and may lead to an increased risk of severe disease (DHF/DSS).

Treatment of dengue fever is based solely on symptoms and signs, with fluid replacement required for severe fever and hemorrhagic or shock cases. No antiviral therapy for dengue virus infection is available. Preventive measures that rely on mosquito control and individual protection, are of limited efficacy, complex to implement and questionable in terms of cost-effectiveness. There is a great unmet global public health need for a safe and effective vaccine that will protect against dengue infection, and thereby reduce the morbidity and mortality associated with dengue disease [1-7]. A tetravalent dengue vaccine (CYD-TDV) has been recently approved in some countries in Asia and Latin America [8]. However, the initial findings suggest an unfavorable risk-benefit profile for younger subjects with the approved vaccine. Vaccine efficacy was different between serotypes and depended on dengue baseline seropositivity status. Hence, there is a continued unmet public health need for safer and more efficacious dengue vaccines. Additional vaccines are also important to ensure sufficient supply globally [9, 10].

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

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

the wild type virus strains, TDV-1 16007, TDV-3 16562 or TDV-4 1036 virus, respectively [12]. TDV is thus comprised of four recombinant, live attenuated dengue virus strains: a molecularly characterized, attenuated DEN-2 strain (TDV-2), a DEN-2/1 chimera (TDV-1), a DEN-2/3 chimera (TDV-3) and a DEN-2/4 chimera (TDV-4).

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

Data from two Phase I trials and a Phase II trial show satisfactory reactogenicity, safety and immunogenicity of Takeda's TDV in adults living in non endemic areas as well as in adults and children living in dengue endemic areas in Asia and Latin America. The investigational vaccine (lyophilized[CCI] formulations) used in the Phase I and Phase II, which is a tetravalent dengue vaccine comprised of four recombinant, live attenuated dengue virus strains [CCI] of TDV-1, TDV-2, TDV-3 and TDV-4, respectively, generated a predominant immune response against DENV-2 and a relatively low immune response to DENV-4. For this reason, we will reduce the dose of only TDV-2 [CCI]) in order to better balance the immune response to the four serotypes. The TDV dose formulation will be [CCI] plaque forming units (PFU) of TDV-1, TDV-2, TDV-3 and TDV-4, respectively, vaccination schedule (one dose of vaccine), and route of administration (subcutaneous [SC] route) [CCI]

Refer to the current Investigator Brochure of Takeda's TDV contains additional product information and a more detailed review of pre-clinical and clinical studies [13].

4.2 Rationale for the Proposed Trial

Data generated to date show that the major part of the immune response to Takeda's TDV occurs after the first dose, with the second dose having only a limited effect on geometric mean titers. Although this observation could suggest that a single dose of TDV may be sufficient, data on the persistence of immune responses after a single dose are limited by the administration of a second dose at 3 months. This trial will therefore assess the immune responses for up to 48 months after a single dose. Additional groups of subjects will either receive a 2 dose schedule (Month 0 and Month 3) or a booster vaccination given at Month 12. These 3 groups will enable a descriptive comparison of the immune responses to Takeda's TDV given as either a 2 dose primary series or as a 1 primary dose with and without a booster at Month 12.

The trial will be conducted in subjects aged 2 to <18 years living in dengue endemic countries [CCI] A total of 600 subjects (groups 1 and 4: 100 subjects each; groups 2 and 3: 200 subjects each) is considered sufficient for immunogenicity

assessments and is defined as immunogenicity subset. In order to limit the number of subjects with repeated blood sampling, fewer subjects are randomized into the immunogenicity subset from group 1 (which acts as a 2 dose immunogenicity control for the groups receiving 1 dose with or without a booster) and from group 4 (which acts as a safety control for the groups receiving TDV). Fewer group 1 and group 4 subjects in the immunogenicity subset also prevents the defacto unblinding that would result from all 200 subjects in those groups being included in the subset. Subjects included in the immunogenicity subset will be randomly selected using the Interactive Web/Voice Response System (IWRS/IVRS). CCI [redacted]

Enrollment into each of the 4 groups is unbalanced such that the groups receiving a schedule likely to be taken into the Phase III studies are over-represented.

In order to maintain the double blind design, a placebo injection (Phosphate Buffered Saline [PBS]) will be used at the appropriate time points. Outside the context of this trial, a licensed vaccine will be offered to all subjects, irrespective of their full participation in this trial and at least 18 months after the first protocol defined vaccination to provide benefit to the participants. The choice of this vaccine will be discussed by medical monitor with each investigator and will need to be approved by the appropriate ethics committee. This vaccine will be used according to the registered indication in the country(ies).

Safety will be assessed in all subjects throughout the trial. This will include the collection of serious adverse events (SAEs) and identification of febrile episodes of potential dengue etiology. Detailed reactogenicity as well as unsolicited adverse events (AEs) up to 28 days after each vaccination (including day of vaccination) will only be assessed in subjects included in the immunogenicity subset.

The trial will be conducted in accordance with the protocol, ICH-GCP Guidelines, 21 CFR Part 56 & 50 and any other applicable regulatory requirements.

5.0 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

- To assess the humoral immune responses to subcutaneously administered TDV in a subset of healthy subjects aged between 2 and <18 years and living in dengue endemic countries.

5.1.2 Secondary Objectives

Immunogenicity:

- To assess seropositivity rates following subcutaneously administered TDV in a subset of healthy subjects aged between 2 and <18 years and living in dengue endemic countries.

Safety:

- To evaluate the safety of subcutaneously administered TDV in healthy subjects aged between 2 and <18 years and living in dengue endemic countries.

5.1.3 Exploratory Objective

- CCI [redacted]

5.2 Endpoints

5.2.1 Primary Endpoint

- Geometric Mean Titers (GMTs) of neutralizing antibodies (microneutralization test [MNT_{50}]) for each of the four DENV serotypes at Months 1, 3, 6, 12, 13, 18, 24, 36, and 48.

5.2.2 Secondary Endpoints

Immunogenicity:

- Seropositivity rates (%)for each of the four DENV serotypes where seropositivity (MNT_{50}) is defined as a reciprocal neutralizing titer ≥ 10 at Months 1, 3, 6, 12, 13, 18, 24, 36, and 48.

Safety:

Immunogenicity subset:

- Frequency and severity of solicited local (injection site) and systemic AEs for 7 and 14 days after each vaccination, respectively.
- Percentage of subjects with any unsolicited AEs for 28 days after each vaccination.

All Subjects:

- Percentage of subjects with SAEs throughout the trial.

- Percentage of subjects with febrile episodes of virologically confirmed dengue throughout the trial.

5.2.3 Exploratory Endpoints

CCI

[redacted]

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial Design

This is a Phase II, double-blind, controlled, randomized trial that will enroll 1,800 healthy children aged 2 to <18 years old into 1 of 4 treatment groups:

- **Group 1 (TDV 2-dose)**: receiving a two-dose primary vaccination at Day 1 (M0) and Day 91 (M3) with the trial vaccine. These subjects will also receive a placebo injection at Day 365 (M12).
- **Group 2 (TDV 1-dose)**: receiving a one-dose primary vaccination at Day 1 (M0) with the trial vaccine. These subjects will also receive a placebo injection at Day 91 (M3) and Day 365 (M12).
- **Group 3 (TDV 1-dose with booster)**: receiving a one-dose primary vaccination at Day 1 (M0) and booster vaccination at Day 365 (M12) with the trial vaccine. These subjects will also receive a placebo injection at Day 91 (M3).
- **Group 4 (Placebo Control)**: receiving injections of placebo at Day 1 (M0), Day 91 (M3), and at Day 365 (M12)

Subjects will be randomized to these groups in a 1:2:5:1 ratio as shown in Table 6.a.

Randomization will be stratified by age group based on the age at the time of informed consent: (1) 2 to 5 years of age, inclusive, (2) 6 to 11 years of age, inclusive, and (3) 12 to <18 years of age

CCI [redacted]

Table 6.a Number of Subjects Per Group

Group	No. of subjects	No. of subjects in the immunogenicity subset
Group 1	200	100
Group 2	400	200
Group 3	1,000	200
Group 4	200	100
Total	1,800	600

- Safety evaluation will include documentation of SAEs and identification of febrile episodes of potential dengue etiology in all subjects for the trial duration. In addition, all subjects in the immunogenicity subset will be provided with a diary card and will be instructed to record:
  - Solicited local adverse events (AEs) for 7 days following vaccination (day of vaccination + 6 days). These will include:
    - infant/toddler/child < 6 years: injection site pain, injection site erythema and injection site swelling.

  - adult and child (≥ 6 years): injection site pain, injection site erythema and injection site swelling.

- Solicited systemic AEs for 14 days following vaccination (day of vaccination + 13 days). These will include:
  - infant/toddler/child < 6 years: fever, irritability/fussiness, drowsiness and loss of appetite.
  - adult and child (≥ 6 years): asthenia, fever, headache, malaise, myalgia.
- Unsolicited AEs for 28 days following vaccination (day of vaccination + 27 days).

- Any subject with febrile illness (defined as temperature ≥ 38°C on 2 consecutive days) will be asked to return to the site for dengue fever evaluation. A dengue infection will be considered virologically confirmed by either positive polymerase chain reaction (PCR) or NS1 enzyme-linked immunosorbent assay (ELISA). A blood sample will be collected within ≤ 5 days after the onset of fever to perform virological confirmation of dengue (approximately 4 ml) and for haematology (white cell count [WCC] and differential, platelet cell count [PCT] and hematocrit [HCT]) and biochemistry (aspartate transamininase [AST] and alanine transaminase [ALT]) to assess the severity of infection. Hematology and biochemistry will be performed by local laboratories and the volume will depend on local laboratory needs (typically 5 ml or less).
- Blood samples for the measurement of neutralizing antibodies (immunogenicity) will be collected as shown in Table 6.a from a randomly selected subset of 600 subjects (100 subjects in group 1 and group 4 and 200 subjects in group 2 and group 3). CCI [redacted] Samples for immunogenicity will be taken as shown in Table 6.b prior to vaccination and at intervals of 1, 3, 6, 12, 13, 18, 24, 36, and 48 months following the first vaccination. CCI [redacted] The rationale and volume of blood samples are given in Table 6.c.

Table 6.b Timing of Vaccination and Blood Sampling for Immunological Testing

Month	M 0	M 1	M 3	M 6	M 12	M 13	M 18	*M 24*	*M 36*	*M 48*
Group 1	S V	S	S V	S	S V*	S	S	*S*	*S*	*S*
Group 2	S V	S	S V*	S	S V*	S	S	*S*	*S*	*S*
Group 3	S V	S	S V*	S	S V	S	S	*S*	*S*	*S*
Group 4	S V*	S	S V*	S	S V*	S	S	*S*	*S*	*S*

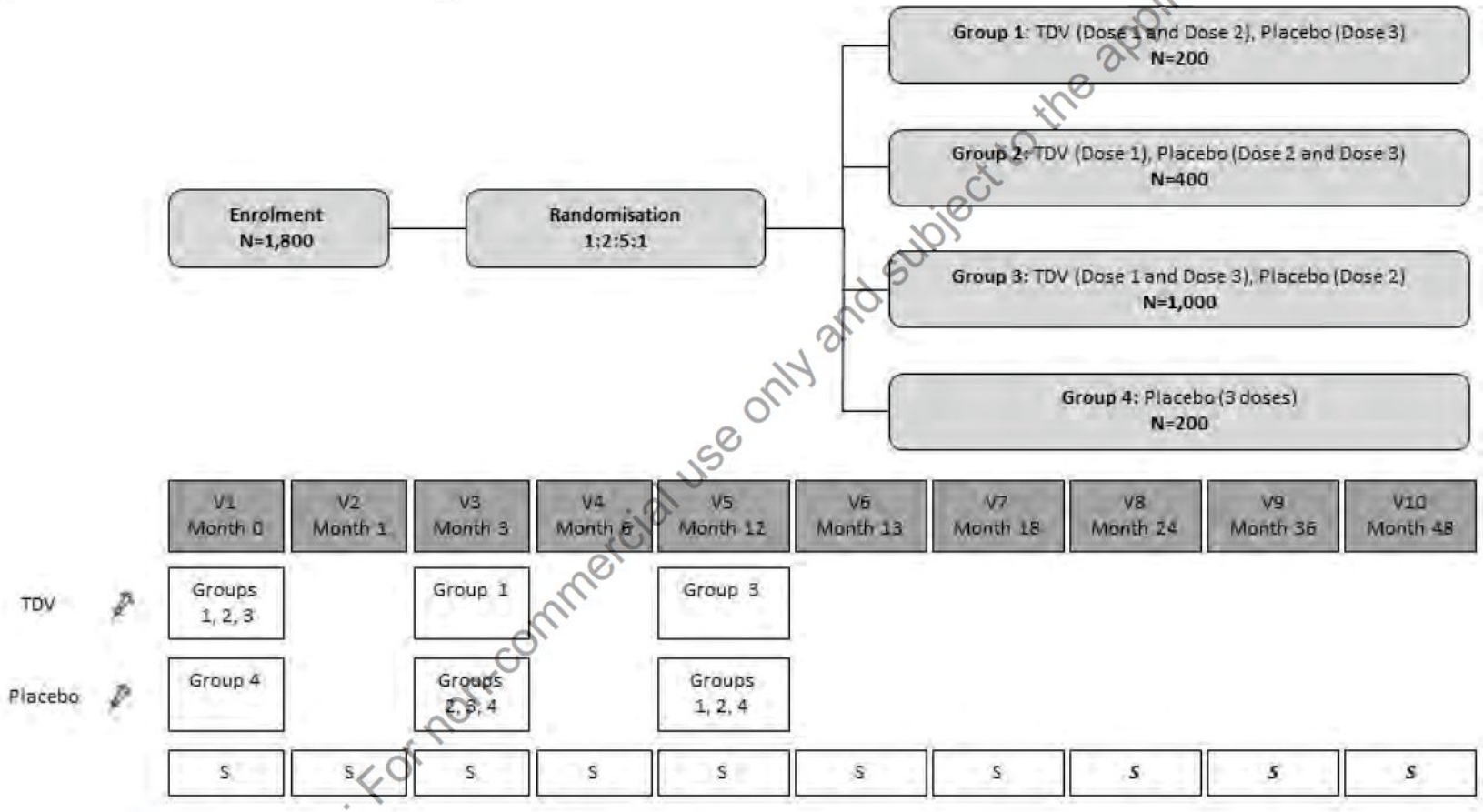
V = vaccination (TDV)
V* = vaccination (placebo)
S = blood sample for immunogenicity[CCI]

Table 6.c Timing of Vaccination and Blood Sampling for Immunological Testing

Population	Reason for blood sample	Approximate volume of blood	Number of visits in which blood is taken	Total volume of blood
Immunogenicity subset (600 subjects)	Measurement of neutralizing antibodies	4 ml	10	40 ml
[CCI]				
All subjects with an acute febrile illness	Virological confirmation of dengue infection	4 ml	unscheduled	7 to 9 ml per febrile episode
	Clinical assessment of potential dengue infection	3 to 5 ml depending on local laboratory		

- For each subject, the duration of the trial will be 48 months and will include a total of 10 protocol-scheduled visits for subjects included in the immunogenicity subset and a total of 7 protocol-scheduled visits for subjects not included in the immunogenicity subset.
- Data collection: electronic Case Report Form (eCRF).
- Interim analyses on cleaned safety and immunogenicity data [CCI] are planned on data up to Month 6, and on data up to Month 18.

Figure 6.a Schematic of Trial Design



V = Visit
S = Blood sample for immunogenicity; [redacted]
Note: for subjects not included in the immunogenicity subset, study visits will be performed at Months 0, 3, 12, 18, 24, 36, and 48

6.2 Justification for Trial Design, Dose, and Endpoints

The trial design and the collection of solicited and unsolicited AEs following vaccination are consistent with vaccine evaluation studies.

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

The trial will be conducted in subjects aged 2 to <18 years living in dengue endemic countries in order to support a large scale Phase III efficacy trial in a similar population.

CCI [redacted] Refer to Section 13.3.

A total of 600 subjects (groups 1 and 4: 100 subjects each; groups 2 and 3: 200 subjects each) are considered sufficient for immunogenicity assessments. CCI [redacted]

Enrollment into each of the 4 groups is unbalanced such that the groups receiving a schedule likely to be taken into the Phase III studies are over-represented.

In order to maintain the double blind design, a placebo vaccine (PBS) will be used at the appropriate time points.

Refer to the current Investigator's Brochure of Takeda's TDV for additional product information and a more detailed review of pre-clinical and clinical studies [13].

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

The duration of the trial will be 48 months for each subject.

6.4 Premature Termination or Suspension of Trial or Investigational Site

6.4.1 Criteria for Premature Termination or Suspension of the Trial

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

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

6.4.2 Criteria for Premature Termination or Suspension of Investigational Sites

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

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

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

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

All entry criteria, including test results, need to be confirmed prior to randomization.

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria:

1. The subject is aged 2 to <18 years, at the time of enrollment
2. Individuals are in good health at the time of entry into the trial as determined by medical history, physical examination (including vital signs), and clinical judgment of the investigator.
3. The subject or, when applicable, the subject's legally acceptable representative signs and dates a written, informed consent form (and assent form, where required) and any required privacy authorization prior to the initiation of any trial procedures, after the nature of the trial has been explained according to local regulatory requirements (Appendix C).
4. Individuals 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. Febrile illness (temperature ≥ 38°C or 100.4°F) or moderate or severe acute illness or infection at the time of enrollment. Trial entry should be delayed until the illness has improved.
2. Individuals with history or any illness that, in the opinion of the investigator, might interfere with the results of the trial or pose additional risk to the subjects due to participation in the trial, including but not limited to:
    a. Known hypersensitivity or allergy to any of the vaccine components.
    b. Female subjects who are pregnant or breastfeeding.
    c. Individuals with any serious chronic or progressive disease according to judgment of the investigator (e.g. neoplasm, insulin-dependent diabetes, cardiac, renal or hepatic disease, neurologic or seizure disorder or Guillain-Barré syndrome).
    d. Known or suspected impairment/alteration of immune function, including:
        i. Chronic use of oral steroids (Equivalent to 20 mg/day prednisone ≥ 12 weeks / ≥ 2 mg/kg body weight / day prednisone ≥ 2 weeks) within 60 days prior to Day 1 (use of inhaled, intranasal, or topical corticosteroids is allowed).
        ii. Receipt of parenteral steroids (Equivalent to 20 mg/day prednisone ≥ 12 weeks / ≥ 2 mg/kg body weight / day prednisone ≥ 2 weeks) within 60 days prior to Day 1.

iii. Administration of immunoglobulins and/or any blood products within the three months preceding the first administration of the investigational vaccine or planned administration during the trial.

iv. Receipt of immunostimulants within 60 days prior to Day 1.

v. Immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy within 6 months preceding (first) vaccination.

vi. HIV infection or HIV-related disease.

vii. Genetic immunodeficiency.

3. Individuals who 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 of investigational vaccine administration.
4. Individuals participating in any clinical trial with another investigational product 30 days prior to first trial visit or intent to participate in another clinical trial at any time during the conduct of this trial.
5. Individuals who participated in a previous dengue vaccine trial.
6. Individuals who are first degree relatives of individuals involved in trial conduct.
7. If female of childbearing potential, sexually active, and has not used any of the "acceptable contraceptive methods" for at least 2 months prior to trial entry:
    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), bilateral tubal ligation (at least 1 year previously), bilateral oophorectomy (at least 1 year previously) or hysterectomy.
    b. Acceptable birth control methods are defined as one or more of the following:
        i. Hormonal contraceptive (such as oral, injection, transdermal patch, implant, cervical ring).
        ii. Barrier (condom with spermicide or diaphragm with spermicide) each and every time during intercourse.
        iii. Intrauterine device (IUD).
        iv. Monogamous relationship with vasectomized partner. Partner must have been vasectomized for at least six months prior to the subjects' trial entry.
        v. Sexual abstinence agreement
8. If female of childbearing potential, sexually active and refuses to use an "acceptable contraceptive method" through to 6 weeks after the last dose of investigational vaccine.

There may be instances when individuals meet all entry criteria except one that relates to transient clinical circumstances (e.g., body temperature elevation or recent use of excluded medication or

vaccine). Under these circumstances, a subject may be considered eligible for trial enrollment if the appropriate window for delay has passed, inclusion/exclusion criteria have been rechecked, and if the subject is confirmed to be eligible.

7.3 Criteria for Delay of Vaccination

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

- Individuals with a body temperature >38.0°C (>100.4°F) within 3 days of intended trial vaccination.
- Individuals who have received blood, blood products and/or plasma derivatives or any parenteral immunoglobulin preparation in the past 3 months.
- Individuals who received any other vaccines within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to enrolment in this trial or who are planning to receive any vaccine within 28 days of last vaccination.

There are also circumstances under which receipt of further vaccines is a contraindication in this trial. These circumstances include anaphylaxis or severe hypersensitivity reactions following the initial vaccination. If these reactions occur, the subject must not receive additional vaccinations but is encouraged to continue in trial participation for safety reasons.

7.4 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the trial should be recorded in the [electronic] case report form ([e]CRF) using the following categories. For screen failure subjects, refer to Section 9.1.12.

1. Protocol violation: The subject may remain in the trial unless continuation in the trial jeopardizes the subject's health, safety or rights.
2. Adverse Event: The subject has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue because of the AE.
3. Lost to follow-up: The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented.
4. Withdrawal by subject: The subject (or subject's legally acceptable representative) wishes to withdraw from the trial. The reason for withdrawal, if provided, should be recorded in the eCRF.

   Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (i.e., withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category).

5. Trial termination by:
    a. The sponsor.
    b. The IRB.
    c. The IEC.
    d. The regulatory agency.
6. Pregnancy: Any subject who, despite the requirement for adequate contraception, becomes pregnant during the trial will not receive further investigational vaccines. The site should maintain contact with the pregnant subject and complete a "Clinical Trial Pregnancy Form" as soon as possible. In addition, the subject should be followed-up until the birth of the child, or spontaneous or voluntary termination; when pregnancy outcome information becomes available, the information should be captured using the same form. The subject should be reported as a withdrawal from trial and the reason for withdrawal (e.g. pregnancy) recorded in detail on the Trial Termination" eCRF and subject' medical records.
7. Other.

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

7.5 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may terminate a subject's trial participation at any time during the trial when the subject meets the trial termination criteria described in Section 7.4. In addition, a subject may discontinue his or her participation without giving a reason at any time during the trial. Should a subject's participation be discontinued, the primary criterion for termination must be recorded. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit. Discontinued or withdrawn subjects will not be replaced.

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

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

8.0 INVESTIGATIONAL VACCINE(S) AND MATERIALS

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

8.1 Investigational Vaccine(s) and Materials

The investigational vaccine (lyophilized CCI formulations) is a tetravalent dengue vaccine comprised of four recombinant, live attenuated dengue virus strains: CCI of TDV-1, TDV-2, TDV-3 and TDV-4, respectively.

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

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

CCI

8.1.1.1 Sponsor-Supplied Vaccines

Vaccines described in this protocol will be supplied by the sponsor. The prefilled vials will be supplied in single dose cartons. Active kits will also contain Water For Injection (WFI) as diluent. Each kit will contain a label that includes pertinent trial information and caution statements. The label text will be in the specific country language, depending on local requirements. The vaccine to be used will be identifiable by a unique identification number and managed by the interactive web/voice response system (IWRS/IVRS).

- **Investigational Vaccine (TDV)**

The lyophilized investigational vaccine is presented in a labeled, single-use, CCI with a CCI stopper and CCI that once reconstituted will contain a single 0.5 ml liquid dose for subcutaneous injection.

TDV will be reconstituted by adding 0.7 ml WFI to facilitate withdrawal of one dose (0.5 ml).

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

- **Placebo**

The Placebo will be Phosphate Buffered Saline and will be provided in either 0.7 or 2 ml vials for 0.5 ml dosing. This will be provided by the sponsor in a uniquely numbered carton and will be dispensed by the interactive web/voice response system (IWRS/IVRS).

Refer to Section 8.4 for investigational vaccine blind maintenance.

8.1.2 Storage

Vaccine will be shipped in refrigerated containers.

From receipt and prior to use, the lyophilized CCI vaccine must be protected from light and stored at +2°C to +8°C in a refrigerator.

All clinical trial material must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. All sponsor-supplied vaccines must be stored under the conditions specified on the label, and remain in the original container until administered. A daily temperature log of the vaccine storage area must be maintained every working day.

Temperature deviations must be reported to the sponsor or delegate; see the Pharmacy Manual for instructions.

8.1.3 Dose and Regimen

The dosages for the sponsor-supplied investigational vaccines are presented in Table 8.a.

Table 8.a Sponsor-Supplied Investigational Vaccines

Group	Day 1 (M0)	Day 91 (M3)	Day 365 (M12)	Subjects
1	TDV	TDV	Placebo	200
2	TDV	Placebo	Placebo	400
3	TDV	Placebo	TDV	1,000
4	Placebo	Placebo	Placebo	200

8.2 Investigational Vaccine Assignment and Dispensing Procedures

The investigator or investigator's designee will access the IWRS/IVRS on Day 1 (M0) to obtain the subject number.

The investigator or investigator's designee will utilize the IWRS/IVRS to randomize the subject into the trial, including assignment into the immunogenicity subset. During this contact, the investigator or designee will provide the necessary subject identifying information.

The vaccine ID number of the kit to be administered will be assigned by the IWRS/IVRS.

The vaccination will be prepared and administered by the unblinded designee according to the instructions in the Pharmacy Manual.

All vaccines will be administered subcutaneously in the subject's preferably non-dominant arm. In toddlers, the vaccine may be given in the anterolateral thigh or per local practice. Expired vaccines must not be administered.

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. All

vaccines will be administered only by unblinded personnel who are qualified to perform that function under applicable laws and regulations for that specific trial.

If sponsor-supplied vaccine is lost or damaged, the site can request a replacement from the IWRS/IVRS (refer to IWRS/IVRS manual supplied separately). At subsequent vaccine-dispensing visits, the investigator or designee will again contact the IWRS/IVRS to request additional investigational vaccine for a subject.

8.2.1 Precautions to be Observed in Administering the Investigational Vaccine

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

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

Investigational vaccines should not be administered to subjects with known hypersensitivity to any component of the vaccines.

Standard immunization practices are to be observed, and care should be taken to administer the injection appropriately. Before administering the vaccine, the vaccination site is to be disinfected with a skin disinfectant (e.g., 70% alcohol). Allow the skin to dry. DO NOT inject intravascularly or intramuscularly.

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

8.3 Randomization Code Creation and Storage

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

Randomization will be stratified by age group based on the age at the informed consent: (1) 2 to 5 years of age, inclusive, (2) 6 to 11 years of age, inclusive, and (3) 12 to <18 years of age[CCI] [redacted] Subjects included in the immunogenicity subset will be randomly selected using the Interactive Web/Voice Response System (IWRS/IVRS).

8.4 Investigational Vaccine Blind Maintenance

This is a blinded trial. The subjects, data collectors (e.g., investigator), and data evaluators (e.g., trial statisticians) are blinded. One or more designated pharmacists/ vaccine administrators will be

unblinded at the site. These unblinded designees will maintain the investigational vaccine blind and will have no role in the assessment of subject safety.

8.5 Unblinding Procedure

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

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

The sponsor's Pharmacovigilance Department must be notified as soon as possible if the investigational vaccine blind is broken by the investigator for the purposes of a medical emergency, and if appropriate a completed SAE form must be sent within 24 hours. The date, time, and reason the blind was broken must be recorded in the source document and the same information (except the time) must be recorded on the eCRF.

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

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

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

The investigator or designee must ensure that the sponsor-supplied vaccine is used in accordance with the approved protocol and is administered only to subjects enrolled in the trial. To document appropriate use of sponsor-supplied vaccine, the investigator must maintain records of all sponsor-supplied vaccine delivery to the site, site inventory, dispensation, and use by each subject, and return to the sponsor or designee as noted below.

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

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

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

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

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

The investigator must record the current inventory of all sponsor-supplied vaccines on a sponsor-approved vaccine accountability log. The following information will be recorded at a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied vaccines, expiry and/or retest date and number of doses administered including initials of the person dispensing the vaccine. The log should include all required information as a separate entry for each subject to whom sponsor-supplied vaccine is dispensed. The IWRS/IVRS will include all required information as a separate entry for each subject who is administered sponsor-supplied vaccine.

The investigator will be notified of any expiry date or retest date extension of clinical trial material during the trial conduct if applicable. On expiry date notification from the sponsor or designee, the site must complete all instructions outlined in the notification, including segregation of expired clinical trial material for return to the sponsor or its designee for destruction.

Prior to site closure or at appropriate intervals throughout the trial, before any clinical trial materials are returned to the sponsor or its designee for destruction, a representative from the sponsor or its designee will perform clinical trial material accountability and reconciliation. The investigator will retain a copy of the documentation regarding clinical trial material accountability, return, and/or destruction, and originals will be sent to the sponsor or designee.

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

9.0 TRIAL PLAN

9.1 Trial Procedures

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

9.1.1 Informed Consent/Assent Procedure

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

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

A unique identification number (screening number) will be assigned to each subject after informed consent/informed assent is obtained from the IWRS/IVRS. If all eligibility criteria are fulfilled, this will become the definitive subject number to be used throughout the trial. Subject numbers assigned to subjects who fail screening should not be reused (Section 9.1.12).

9.1.2 Demographics, Medical History and Medication History Procedure

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

Medical History will also be collected for all subjects and recorded in the subject's source document. This includes but is not limited to any medical history that may be relevant to subject eligibility for trial participation such as previous and ongoing illnesses or injuries. Relevant medical history can also include any medical history that contributes to the understanding of an AE that occurs during trial participation, if it represents an exacerbation of an underlying disease/pre-existing problem.

The use of antipyretics and/or analgesic medications within 24 hours prior to vaccination by subjects in the immunogenicity subset must be identified and the reason for their use (prophylaxis versus treatment) must be described in the source documents and the eCRF.

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.

Assess and record in the subject's source document concomitant therapy and vaccine history from 4 weeks prior to administration of each dose of TDV or placebo, as applicable, and ending one month (minimum 28 days) after the last dose of TDV or placebo. Additionally, the receipt of any dose of any licensed dengue vaccine should be recorded throughout the trial.

Prohibited Therapies (Refer to Section 7.2):

1. Receipt of a vaccine outside of the conditions allowed in exclusion criteria No 3, No 4 and No 5.

2. Parental immunoglobulin preparation or blood products within 3 months of the first vaccination and during the trial.
3. Immunosuppressive therapy within 6 months or systemic (e.g. oral or parenteral) corticosteroid treatment within 60 days prior to investigational vaccine administration.

   These data must be written in the source documents.

Medical history to be obtained will include any significant conditions or diseases that have disappeared or resolved at or prior to signing of informed consent/informed assent.

9.1.3 Documentation of Trial Entrance/Randomization

Only subjects who have signed, or had signed on their behalf, the informed consent/informed assent form, meet all of the inclusion criteria and none of the exclusion criteria are eligible for entrance/randomization into the vaccination phase. The list of randomization assignments is produced by IWRS/IVRS.

Randomization will be stratified by age group based on the age at the time of informed consent: (1) 2 to 5 years of age, inclusive, (2) 6 to 11 years of age, inclusive, and (3) 12 to <18 years of age and CCI [redacted]

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

9.1.4 Physical Examination Procedure

Physical examinations must be performed by a qualified health professional in accordance with local regulations and licensing requirements designated within the Site Responsibility Delegation Log. Complete physical examination will be performed on Month 0. A detailed physical examination includes but is not limited to: auscultation of heart and lungs, palpation of the abdomen, inspection of extremities (including skin over intended vaccination site(s)), and a check of general appearance. Additional physical examination procedures may be performed if indicated by review of the subject's medical history. Document the findings in the subject's source document.

A brief symptom-directed physical examination may be performed during the clinic visits.

9.1.5 Vital Signs

During the physical examination, a subject should have their vital signs measured. These will include systolic blood pressure/diastolic blood pressure, heart rate, body temperature, height and weight.

Refer to the Procedures Manual.

9.1.6 Immunogenicity [CCI] Assessments

Subjects included in the immunogenicity subset (100 subjects in group 1 and group 4 and 200 subjects in group 2 and group 3) will undergo blood sampling for serological immunogenicity testing at Months 0, 1, 3, 6, 12, 13, 18, 24, 36, and 48.

[CCI]

The maximum amount of blood in any 8 week period will be 3 ml/kg or 50 ml (whatever is lower), as recommended by Partners Human Research Committee and the US Office for Human Research Protection.

All samples will be collected in accordance with acceptable laboratory procedures. The maximum amount of blood taken at any single visit is approximately 24 ml, and the approximate total volume of blood for immunogenicity assessments for the trial is maximum 40 ml for the immunogenicity subset [CCI] Should a subject experience an acute febrile illness (defined as temperature ≥ 38°C on 2 consecutive days), additional blood (approximately 9 ml) will be taken for the assessment of potential dengue infection. The total blood volume for these unscheduled visits depends on the number of acute febrile episodes experienced by an individual subject.

Blood sample processing and storage will be detailed in the Laboratory Guidelines, as provided in the Procedures Manual.

9.1.7 Safety Assessments

Solicited Safety Parameters

The occurrence of selected indicators of reactogenicity (Table 9.a), unless otherwise defined, will be measured/collected for subjects included in the immunogenicity subset until Day 7 (day of vaccination + 6 subsequent days) for local solicited AEs and until Day 14 (day of vaccination + 13 subsequent days) for systemic solicited AEs and will be recorded on the "Local and Systemic Reactions" eCRF, as applicable. These will be summarized in the final report under the category "solicited adverse events" to differentiate them from other AEs which were not solicited. Any solicited local or systemic AE observed as continuing on Trial Day 8 or 15, respectively, will be recorded as an AE on the Adverse Event eCRF.

Table 9.a Solicited Local and Systemic AEs

	Infant/Toddler (15–24 months)/Child (< 6 years)	Adult and child (≥ 6 years)
Local AEs (injection site):	Pain	Pain
	Erythema	Erythema
	Swelling	Swelling
Systemic AEs:	Fever[a]	Fever[a]
	Irritability/fussiness	Asthenia
	Drowsiness	Headache
	Loss of appetite	Malaise
		Myalgia

(a) Body temperature ≥ 38°C or 100.4°F is defined as fever irrespective of site of measurement

Any unsolicited AEs will be collected for 28 days following each dose.

SAEs and febrile episodes of potential dengue etiology will be collected from the time that the subject is first administered the investigational vaccine (Month 0) up to the end of the trial (Month 48).

The intensity of solicited AEs will be assessed as described in Table 9.b and Table 9.c.

Table 9.b Intensity Scales for Solicited AEs in Infants/Toddlers (15-24 Months)/Child (< 6 Years)

Infant/Toddler (15–24 months)/Child (< 6 years)		
Adverse Event	**Intensity grade**	**Severity/Intensity**
Pain at injection site	0	None
	1	Mild: Minor reaction to touch
	2	Moderate: Cries/protests on touch
	3	Severe: Cries when limb is moved/spontaneously painful
Erythema at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever[a]		Record body temperature in °C/°F
Irritability/Fussiness	0	Behavior as usual
	1	Mild: Crying more than usual/no effect on normal activity
	2	Moderate: Crying more than usual/interferes with normal activity
	3	Severe: Crying that cannot be comforted/prevents normal activity
Drowsiness	0	Behavior as usual
	1	Mild: Drowsiness easily tolerated
	2	Moderate: Drowsiness that interferes with normal activity
	3	Severe: Drowsiness that prevents normal activity
Loss of appetite	0	Appetite as usual
	1	Mild: Eating less than usual/no effect on normal activity
	2	Moderate: Eating less than usual/interferes with normal activity
	3	Severe: Not eating at all

(a) Body temperature ≥ 38°C or 100.4°F is defined as fever irrespective of site measurement

Table 9.c Intensity Scales for Solicited AEs in Adults/Children (≥ 6 Years)

Adults/Child (≥ 6 years)		
Adverse Event	**Intensity grade**	**Severity/Intensity**
Pain at injection site	0	None
	1	Mild: Any pain neither interfering with nor preventing normal every day activities.
	2	Moderate: Painful when limb is moved and interferes with every day activities.
	3	Severe: Significant pain at rest. Prevents normal every day activities.
Erythema at injection site		Record greatest surface diameter in mm
Swelling at injection site		Record greatest surface diameter in mm
Fever[a]		Record body temperature in °C/°F
Headache	0	Normal
	1	Mild: Headache that is easily tolerated
	2	Moderate: Headache that interferes with normal activity
	3	Severe: Headache that prevents normal activity
Asthenia	0	Normal
	1	Mild: Asthenia that is easily tolerated
	2	Moderate: Asthenia that interferes with normal activity
	3	Severe: Asthenia that prevents normal activity
Malaise	0	No symptoms
	1	Mild: Malaise that is easily tolerated
	2	Moderate: Malaise that interferes with normal activity
	3	Severe: Malaise that prevents normal activity
Myalgia	0	No symptoms
	1	Mild: Myalgia that is easily tolerated
	2	Moderate: Myalgia that interferes with normal activity
	3	Severe: Myalgia that prevents normal activity

(a) Body temperature ≥ 38°C or 100.4°F is defined as fever irrespective of site of measurement

9.1.8 Febrile illness follow-up

Any subject with febrile illness (defined as temperature ≥ 38°C on 2 consecutive days) or febrile illness clinically suspected to be dengue by the investigator will be asked to return to the site for dengue fever evaluation. A dengue infection will be considered virologically confirmed by either PCR or NS1 ELISA.

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

A blood sample will be collected within (≤) 5 days after the onset of fever to perform virological confirmation of dengue (approximately 4 ml) and for haematology (white cell count and differential, platelet cell count and hematocrit) and biochemistry (AST and ALT) to assess the severity of infection. Haematology and biochemistry will be performed by local laboratories and the volume will depend on local laboratory needs (typically 5 ml or less). Additional investigations (such as chest X-ray, abdominal ultrasound, coagulation tests) are not required by protocol and will be driven by the clinical need.

The subject's medical condition will be recorded in the eCRF, including but not limited to headache, rash, abdominal pain, myalgia, arthralgia, signs of bleeding (including petechiae), signs of plasma leakage. WCC and differential, PCC, HCT, AST and ALT will also be recorded, even if values are normal. Additional investigations performed as part of clinical management will also be recorded in the eCRF if judged as clinically significant by the study physician.

Blood sample processing and storage will be detailed in the Laboratory Guidelines, as provided in the Procedures Manual.

9.1.9 CCI [redacted]

CCI [redacted]

9.1.10 Contraception and Pregnancy Avoidance Procedure

For female subjects of child bearing potential, urine or serum pregnancy testing will be performed prior to vaccination on Day 1 (M0). Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent/informed assent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova. During the course of the trial, regular urine or serum human chorionic gonadotropin (hCG) 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). In addition to a negative urine or serum hCG pregnancy test at Day 1 (M0), subjects also must have a negative urine or serum hCG pregnancy test prior to receiving any dose of investigational vaccine (Day 91/M3 and Day 365/M12).

Refer to Section 7.2.

9.1.11 Pregnancy

To ensure subject safety and the safety of the unborn child, each pregnancy in a subject must be reported to the sponsor within 24 hours of the site learning of its occurrence. If the subject becomes pregnant during the trial, she will not receive any further doses of any sponsor-supplied investigational vaccine/placebo. The pregnancy must be followed to determine outcome, including

spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if the intended duration of safety follow-up for the trial has ended.

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

The investigator must inform the subject of their right to receive treatment information. If the subject chooses to receive unblinded treatment information, the individual blind should be broken by the investigator and procedures must be followed as described in Section 8.5.

9.1.12 Documentation of Subjects who are not Randomized

Investigators must account for all subjects who sign an informed consent or assent. If the subject is found to be not eligible at this visit, the investigator should complete the eCRF. The IWRS/IVRS should be contacted as a notification of non-randomization.

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

- Screen failure (did not meet inclusion criteria or did meet exclusion criteria),
- Withdrawal by subject,
- Trial Terminated by Sponsor,
- Other

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

9.2 Monitoring Subject Treatment Compliance

The investigator must record all injections of investigational vaccine given to the subject in the e(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/time point(s).

9.3.1 Randomization Procedures (Day 1, M0)

- Before performing any other study procedure, the signed informed consent/assent of the subject needs to be obtained. Refer to Section 9.1.1.
- Check inclusion and exclusion criteria. Refer to Sections 7.1 and 7.2.
- Collect demographic data and medical history. Refer to Section 9.1.2.
- "Complete" physical examination (Refer to Section 9.1.4) and body temperature.
- Record height and weight.

- Randomization. Refer to Section 9.1.3.

9.3.2 Vaccination Procedures (Day 1/M0, Day 91/M3, Day 365/M12)

After confirming eligibility and enrolling the subject on Day 1/M0, perform vaccination according to the assigned investigational vaccine and according to the procedures described in Section 8.2. At later clinic visits that involve vaccination (Day 91/M3 and Day 365/M12), confirm that the subject does not meet any criterion for delaying or cancelling additional trial vaccination, as described in Section 6.4.3.

- Record concomitant medication. Refer to Section 9.1.2.
- Perform a pregnancy test for female subjects of child-bearing potential. Refer to Sections 9.1.10 and 9.1.11.
- Check vital signs. Refer to Section 9.1.5.

  A brief symptom-directed physical assessment may be performed, including but not limited to the measurement of vital signs. Corresponding information should be documented in the source documents and eCRFs.
- Check contraindications to vaccination at Day 91/M3 and Day 365/M12. Refer to Section 7.3.
- Collect a blood sample **before vaccination** for the immunogenicity subset. Refer to Section 9.1.6.

  Blood should be taken from the subject using aseptic venipuncture technique. Refer to the detailed collection and handling procedures outlined in the Procedures Manuals.
- Vaccinate according to the assigned investigational vaccine (see Section 8.1.3) and according to the procedures described in Sections 8.2.

9.3.3 Post Vaccination procedures (Day 1/M0, Day 91/M3, Day 365/M12)

The following post-vaccination procedures will be performed for subjects included in the immunogenicity subset:

- Distribute diary cards and perform following procedures:

  Careful training of the subject and the subject's parent/guardian on how to measure local AEs and body temperature, how to complete and how often to complete the diary card. Training should be directed at the individual(s) who will perform the measurements of local AEs and those who will enter the information into the diary card. This individual may not be the subject or the subject's parent/guardian, but if a person other than the subject or the subject's parent/guardian (i.e. caregiver) enters information into the diary card, this person's identity must be documented in the trial file and this person must receive training on the diary card. Training of the subject or the subject's parent/guardian on how to measure an injection site reaction should be performed while the subject is under observation after vaccination.

Diary card instruction must include the following:

- The subject AND/OR the subject's parent/guardian must understand that timely completion of the diary card on a daily basis is a critical component to trial participation. The subject AND/OR the subject's parent/guardian should also be instructed to write clearly and to complete the diary card in pen. Any corrections to the diary card that are performed by the person completing the diary card should include a single strikethrough line with a brief explanation for any change and be initialled. No changes can be made to the diary card when it is returned to the clinic.
- Starting on the day of vaccination, the subject AND/OR the subject's parent/guardian will check in the evening for specific types of reactions at the injection site (solicited local AEs), any specific generalized symptoms (solicited systemic AEs), body temperature (taken preferably orally), any other symptoms or change in the subject's health status, and any medications taken (excluding vitamins and minerals). These solicited AEs and body temperature will be recorded in the diary.
- Body temperature measurement is to be performed, preferably orally, using the thermometer provided by the site. If the subject feels unusually hot or cold during the day, the subject AND/OR the subject's parent/guardian should check body temperature. If the subject has fever, the highest body temperature observed that day should be recorded on the diary card. The measurement of solicited local AEs is to be performed using the ruler provided by the site. The collection of solicited local AEs will continue for a total of 7 days on the diary card. The collection of body temperature and solicited systemic AEs will continue for a total of 14 days (Days 1 to 7 and Days 8 to 14) on the diary card. The collection of unsolicited AEs will continue for a total of 28 days on the diary card.
- After vaccination, the subject will be observed for at least 30 minutes including observation for unsolicited AEs, solicited AEs, and body temperature measurement. Please take the opportunity to remind the subject how to measure solicited reactions and body temperature as part of this observation period. Record all safety data collected in the subject's source documents.
- Injection site evaluation will be performed at 30 minutes after vaccine administration.
- The subject or the subject's parent/guardian will be reminded to complete the diary cards daily and to contact the site if there are any questions.

All subjects or subject's parent/guardian will be given memory cards to serve as a reminder to inform at anytime all AEs, SAEs and febrile episodes to the site during months without a clinic visit.

For the immunogenicity subset, subjects or subject's parent/guardian will be instructed to bring the diary cards at clinic visits at Months 1, 6 and 13. For the post-vaccination 2 diary card, home visits may be done by the site staff in order to collect the diary card. Optionally, a phone call may be made to remind the subject to keep the diary card secure and bring to the site on the Month 6 visit. Site staff will do the safety review with these subjects during these visits.

All subjects or subject's parent/guardian will receive a written reminder of the next planned trial activity and 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 an acute febrile illness or a medical condition that leads to a hospitalization or an emergency room visit or if the subject experiences any sign or symptom perceived as serious. All contact details will be provided to the subject.

9.3.4 Clinic Visits after Vaccination (Month 1, Month 6, Month 13, Month 18, Month 24, Month 36, Month 48)

Clinic Visits that do NOT include a vaccination will be performed on Month 1, Month 6 and Month 13 for subjects included in the immunogenicity subset and for all subjects at Month 18, Month 24, Month 36, and Month 48.

- Record concomitant medication, as applicable. Refer to Section 9.1.2.
- Check vital signs. Refer to Section 9.1.5.

  A brief symptom-directed physical assessment may be performed including but not limited to the measurement of vital signs. Corresponding information should be documented in the source documents and eCRFs.
- Collect a blood sample for the immunogenicity subset. Refer to Section 9.1.6.

  Blood should be taken from the subject using aseptic venipuncture technique. Refer to the detailed collection and handling procedures outlined in the Procedures Manuals.
- For subjects included in the immunogenicity subset, return and transcription of the diary cards at the clinic visits on Months 1, 6 and 13. Relevant safety information, as judged by the investigator, has to be recorded into the subject's source documents and the appropriate eCRF section.
- The receipt of any dose of any licensed dengue vaccine should be recorded using the concomitant medication page of the eCRF.

Please note:

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

- No corrections or additions to the diary card will be allowed after it is delivered to the site.
- Any blank or illegible fields on the diary card will be missing in the eCRF.
- The site must enter all readable entries in the diary card into the eCRF.
- Any illegible or implausible data should be reviewed with the subject or the subject's parent/guardian.

Any newly described safety information (including a solicited reaction) must NOT be written into the diary card and must be described in the trial file as a verbally reported event. Any AE reported in this fashion must be described as an unsolicited event and therefore entered on the AE eCRF.

- The site should schedule the next trial activity clinic visit with subject AND/OR the subject's parent/guardian, as applicable.
- The subject or the subject's parent/guardian will receive a written reminder of the next planned trial activity, as applicable.

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

9.3.5 Phone Contacts – Safety Call

At a minimum, safety calls will be performed:

- For subjects in the immunogenicity and safety group: Months 2, 4, 5, 7-11, 14-17, 19-23, 25-35, 37-47.
- For subjects in the non-immunogenicity group: Months 1, 2, 4-11, 13 to 17, 19-23, 25-35, 37-47.

Additional phone calls for all subjects can be made, as per site specific safety surveillance procedures.

Safety calls are calls made to the subject or subject's parent/guardian/caregiver by a trained healthcare provider. These calls will follow a script which will facilitate the collection of relevant safety information. The subject AND/OR the subject's parent/guardian/caregiver will be interviewed according to the script, and information relating to febrile episodes, SAEs and concomitant medications or vaccinations associated with those events. Additionally, the receipt of any dose of any licensed dengue vaccine should be recorded. All safety information described by the subject must be written down in a designated location within the source documents and not written on the script used for the telephone call. The site should remind the subject AND/OR the subject's parent/guardian/caregiver about the next phone contact or clinic visit. The subject or the subject's parent/guardian/caregiver 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 an acute febrile illness or a medical condition that leads to a hospitalization or an emergency room visit or if the subject experiences any sign or symptom perceived as serious.

9.3.6 Final Visit

The Final Visit will be performed on Month 48 for all subjects as detailed in Section 9.3.4. If a subject terminates earlier, standard visit procedures should be performed if possible. For all subjects, the investigator must complete the End of Trial eCRF page.

9.3.7 Post Trial Care

No post-trial care will be provided except for the provision of a licensed vaccine to all subjects irrespective of their full participation in this trial and at least 18 months after the first protocol defined vaccination. The choice of this vaccine will be discussed between the Sponsor and the Investigator, and will be approved by the appropriate ethics committee. This vaccine will be used according to the labeling approved in the country.

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.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Events (AEs)

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

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

Unsolicited 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

Relatedness to vaccine will also be assessed by the investigator. SAEs will be reported to the sponsor within 24 hours of the investigator becoming aware of the event.

Please note: any solicited AE that meets any of the following criteria must also be entered as an AE on the Adverse Event eCRF.

- Solicited local or systemic AEs leading to the subject withdrawing from the trial.
- Solicited local or systemic AEs lasting beyond 7 days and 14 days, respectively, after vaccination (including day of vaccination).
- Solicited local and systemic AEs that lead to subject being withdrawn from the trial by the investigator.
- Solicited local and systemic AEs that otherwise meet the definition of a serious event (see Section 10.1.5).

10.1.2 Causality of AEs

Relatedness to vaccine will also be assessed by the investigator. The relationship of each AE to investigational vaccine(s) will be assessed using the following categories:

Related: An AE that follows a reasonable temporal sequence from administration of an investigational vaccine, and for which reasonable possible involvement of the investigational vaccine can be argued, although factors other than the investigational vaccine, such as underlying diseases, complications and concomitant drugs, may also be responsible.

Not Related: An AE that does not follow a reasonable temporal sequence from administration of an investigational vaccine and/or that can reasonably be explained by other factors, such as underlying diseases, complications, and concomitant drugs.

10.1.3 Relationship to Trial Procedures

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

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

10.1.4 Additional Points to Consider for AEs

An untoward finding generally may:

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

Diagnoses *vs.* signs and symptoms:

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

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after starting administration of the investigational 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 (e.g., "worsening of…").

- If the subject experiences a worsening or complication of an AE after any change in investigational 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 (e.g., "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/informed assent 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.

Follow Up:

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

10.1.5 Serious Adverse Events (SAEs)

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

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.
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 Procedures

10.2.1 Collection and Reporting of AEs

Please refer to Section 10.2.1.1 for Collection and Reporting of SAEs.

10.2.1.1 AE Reporting

Non-serious AEs will only be collected for subjects in the immunogenicity subset. All subjects included in the immunogenicity subset experiencing AEs within 28 days of each vaccine dose (day of vaccination + 27 days), whether considered associated with the use of the investigational vaccine or not, must be monitored until symptoms subside and any clinically significant abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed. All findings must be reported on an AE eCRF and on the SAE form, if necessary (see Section 10.2.2) which is part of the Investigator Site File. All findings in subjects experiencing AEs must also be reported in the subject's medical records.

The following information will be documented for each event:

- Reported term for the Adverse Event,
- Start and end date,
- Serious (Y/N)?,
- Severity,
- Investigator's opinion of the causality (relationship) between the event and administration of investigational 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 study treatment (investigational vaccine),
- Outcome of event.

10.2.2 Collection and Reporting of SAEs

SAEs will be collected for all subjects. Collection of SAEs will commence from the time that the subject is first administered the investigational vaccine (Month 0). Routine collection of SAEs will continue until the end of the trial (Month 48).

SAEs should be reported according to the following procedure:

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

- A short description of the event and the reason why the event is categorized as serious,

- Subject identification number,
- Investigator's name,
- Name of the investigational vaccine(s) – if no unblinding is necessary, in a blinded way,
- Causality assessment.

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

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately within 24 hours of receipt. Copies of any relevant data from the hospital notes (e.g., laboratory tests, discharge summary, post-mortem results) should be sent to the sponsor.

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

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

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

10.3.2 Post-Trial Events

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

11.0 TRIAL-SPECIFIC REQUIREMENT(S)

11.1 Trial-Specific Committees

11.1.1 Data Monitoring Committee (DMC) Board

Safety oversight will be under the direction of an independent Data Monitoring Committee (DMC) composed of pediatricians and statisticians to protect the ethical and safety interests of recruited subjects, while securing as far as possible the scientific validity of the data. The DMC will be established by the CRO. The DMC will review SAE reports to identify potential treatment harm and all causes of mortality/morbidity.

Responsibilities of the DMC include the following:

- Review of study protocol and protocol amendment(s) with special attention to safety monitoring procedures, and make recommendations for additions or adjustments,
- Review and agree on the sponsor's proposal for presentation of the information needed for review of the safety results, as detailed in the DMC charter,
- Recommendations for study modification or termination for safety reasons.

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, medical history, and concurrent conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDRA [SOC, HLGT, HLT, LL, PT, and their corresponding descriptive terms]). Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 Electronic CRFs (eCRF) and Paper

Completed eCRFs are required for each subject for whom an informed consent/assent is obtained.

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

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

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

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

12.2 Record Retention

The investigator agrees to keep the records stipulated in Section 12.1 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/informed assent forms, electronic copy of eCRFs, including the audit trail, and detailed records of vaccine disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees. Furthermore, International Conference on Harmonization (ICH) E6 Section 4.9.5 requires the investigator to retain essential documents specified in ICH E6 (Section 8) until at least 2 years after the last approval of a marketing application for a specified drug indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the trial records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Trial Site Agreement between the investigator and sponsor.

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

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to the first interim analysis at Month 6. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all trial objectives.

A blinded data review will be conducted prior to unblinding of subject's vaccination assignment. 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

The analysis sets are defined as follows:

Safety Set: The Safety Set will consist of all randomized subjects who received at least one dose of the trial vaccine (including control vaccine). For analyses of solicited AEs and unsolicited non-serious AEs, only subjects in the immunogenicity subset will be included (600 subjects in total [groups 1 and 4: 100 subjects each; groups 2 and 3: 200 subjects each]). SAEs, virologically confirmed dengue and AEs leading to trial or vaccine withdrawal will be assessed for all subjects in the Safety Set.

Full Analysis Set (FAS): The Full Analysis Set will consist of all randomized subjects who received the trial vaccine (including control vaccine) and for whom valid pre-dosing and at least one valid post-dosing blood sample have been received.

Per-Protocol Set (PPS): The Per-Protocol Set will consist of all subjects in the FAS who have no major protocol violations. The major protocol violation criteria will be defined as part of the blinded data review prior to the unblinding of individual subject's treatment assignment. The categories of major protocol violations include: (1) not meeting selected entry criteria, (2) receiving wrong trial treatment, (3) receiving prohibited therapies, and (4) other major protocol violations that may be identified during blinded data reviews.

Both the FAS and PPS will include only subjects from the immunogenicity subset (600 subjects in total [groups 1 and 4: 100 subjects each; groups 2 and 3: 200 subjects each]), i.e., subjects for whom blood samples for assessment of dengue neutralizing antibodies are collected.

The primary analysis of immunogenicity will be based on the PPS, and other supportive analysis may be provided for the FAS. The safety analysis will be based on the Safety Set as described above.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Summaries of age, gender, and other baseline characteristics will be presented by treatment group.

13.1.3 Immunogenicity Analysis

The primary immunogenicity endpoint in the trial is Geometric Mean Titers (GMTs) of neutralizing antibodies (MNT_{50}) for each of the four DEN serotypes. The secondary endpoint is seropositivity rates (%) for each of the four DENV serotypes where seropositivity is defined as a reciprocal neutralizing titer ≥ 10 (MNT_{50}).

For the immunogenicity subset of subjects, descriptive statistics and 95% confidence intervals for both GMT and seropositivity will be computed by treatment group at Months 0, 1, 3, 6, 12, 13, 18, 24, 36, and 48. In addition, the percent of subjects with monovalent, bivalent, trivalent, and tetravalent seropositivity will be summarized by treatment group at each visit. Additional summaries of immunogenicity endpoints by baseline seropositivity status (positive or negative) will also be provided.

CCI [redacted]

13.1.4 Safety Analysis

All summaries of safety data are based on subjects in the Safety Analysis Set. Unless otherwise specified, the safety data will be summarized by treatment group.

Reactogenicity

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

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

Unsolicited Adverse Events

Unsolicited AEs and SAEs, will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) and summarized by system organ class (SOC) and preferred term (PT) for each treatment arm. AEs leading to trial or vaccine withdrawal will also be summarized.

All unsolicited AEs up to 28 days after the last vaccination will be included in the analyses of all AEs. For SAEs and AEs leading to subject withdrawal from the trial, any AE collected during the trial will be included. In general, unsolicited AEs will be tabulated at each of the following levels: overall summary (subject with at least 1 AE) and by SOC and PT. Subjects reporting more than 1 occurrence for the term (level) being summarized will be counted only once. Unsolicited AEs will be summarized as follows: by PT including events with frequency greater than 2%; by SOC and

PT; by SOC, PT, and severity; and by SOC, PT, and relationship to the investigational vaccine. Unless otherwise specified, unsolicited AEs will be summarized in the following 3 ways: 1) overall up to 28 days after each vaccination, 2) with onset between 1 and 14 days after each vaccination, and 3) with onset between 15 and 28 days after each vaccination.

The percentage of subjects with virologically confirmed dengue will also be summarized by treatment group.

13.2 Interim Analysis

Interim analyses on cleaned safety and immunogenicity data [redacted] are planned on data up to Month 6, and on data up to Month 18 to provide data to support the planning and execution of other studies in the development plan of Takeda's TDV. These interim analyses will be performed by a separate set of unblinded statisticians and programmers at the Clinical Research Organization (CRO). They will have access to individual treatment assignments but will not be involved in subsequent trial conduct. The rest of the personnel involved in the conduct of the trial, including those at Takeda, CRO, and the trial sites, will remain blinded to the individual subject data (including treatment assignments) until unblinding after trial completion (database lock for data through the Month 48 Follow Up visit). More details regarding the interim analyses will be provided in the statistical analysis plan.

13.3 Determination of Sample Size

This trial is designed to be primarily 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 will provide a reasonable sample size for the evaluation of the persistence of immune responses following administration of a single TDV dose, and of the effect of a TDV booster dose, and to provide an adequate safety database prior to initiating Phase III studies.

Immunogenicity

For illustrative purposes, Table 13.a provides approximate 95% confidence interval for various different seropositivity rate (MNT_{50}) estimates, given the planned sample size per group in the immunogenicity subset.

Table 13.a Approximate 95% Confidence Interval in Seropositivity Rates (MNT_{50}) Reciprocal Neutralizing Titer ≥ 10) for the Planned Sample Size in the Treatment Groups

Response Rate	(95% CI) N=100		(95% CI) N=200	
	LL	UL	LL	UL
50%	39.8%	60.1%	42.9%	57.1%
60%	49.7%	69.7%	52.9%	66.9%
85%	76.5%	91.4%	79.3%	89.6%

LL = Lower Limit, UL = Upper Limit

For illustrative purposes, Table 13.b provides approximate 95% confidence interval for various different GMT and GSD (Geometric Standard Deviation), given the planned sample size per group in the immunogenicity subset.

Table 13.b Approximate 95% Confidence Interval in GMT of Dengue Neutralizing Antibodies for the Planned Sample Size in the Treatment Group

	(95% CI) N=100		(95% CI) N=200	
GMT (GSD)	**LL**	**UL**	**LL**	**UL**
500 (6)	351.9	710.4	390.1	640.9
1500 (6)	1,055.8	2,131.1	1,170.2	1,922.8
200 (8)	133.1	300.6	149.9	266.8
50 (7)	34.1	73.2	38.2	65.5

LL = Lower Limit, UL = Upper Limit
Note: The GMT and GSD in the table are based on study INV-DEN-203, Day 28 results for serotypes 1-4 in subjects aged 1.5-11 years old (Clinical Study Report Table 15.2.2.7.2)

Safety

Table 13.c illustrates the probability of observing 1 or more event, (e.g., any specific type of AE related to vaccine) for a range of assumed true but unknown event rates in the range of 0.33% to 4.0% (without considering the background incidence).

Table 13.c Probability of Observing 1 or More Events for Assumed "True" Event Rate and Given Sample Size

	Sample Sizes		
"True" Unknown Event Rate	**N=1,600**	**N=1,000**	**N=200**
0.33%	99.5%	96.3%	48.4%
0.50%	>99.9%	99.3%	63.3%
1.00%	>99.9%	>99.9%	86.6%
2.00%	>99.9%	>99.9%	98.2%
3.00%	>99.9%	>99.9%	99.8%
4.00%	>99.9%	>99.9%	>99.9%

N=number of subjects

Therefore, even with an event rate as low as 0.33%, there is a 99.5% chance that at least 1 such event will be observed in the trial. For AEs with event rate higher than 4.00%, there is a >99.9% chance to observe at least one such event.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Trial-Site Monitoring Visits

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

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

14.2 Protocol Deviations

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

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The trial site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the vaccine is stored and prepared, and any other facility used during the trial. In addition, there is the possibility that this trial may be inspected by regulatory agencies, including those of foreign governments (e.g., the FDA, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the trial site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and institution guarantee access for quality assurance auditors to all trial documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE TRIAL

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

15.1 IRB and/or IEC Approval

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

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent/informed assent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent/informed assent must be obtained and submitted to the sponsor or designee before commencement of the trial (i.e., before shipment of the sponsor-supplied Vaccine or trial specific screening activity). The IRB or IEC approval must refer to the trial by exact protocol title, number, and version date; identify versions of other documents (e.g., informed consent/informed assent form) reviewed; and state the approval date. The sponsor will notify the site once the sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the sponsor has received permission from competent authority to begin the trial. Until the site receives [vaccine/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/informed assent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the trial at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

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

15.2 Subject Information and Informed Consent/Informed Assent

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

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

The informed consent/informed assent form 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/informed assent form and subject information sheet 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. In the event the subject is not capable of rendering adequate written informed consent/informed assent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the trial and (2) decide whether or not to participate in the trial. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the trial, then the informed consent/informed assent form must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the trial. The subject or the subject's legally acceptable representative 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/informed assent form at the time of consent and prior to subject entering into the trial; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent/informed assent form 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/informed assent in the subject's medical record. Copies of the signed informed consent/informed assent form and subject information sheet shall be given to the subject.

All revised informed consent/informed assent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent/informed assent. The date the revised consent was obtained should be

recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent/informed assent form.

15.3 Subject Confidentiality

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

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

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

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The results of this trial are expected to be published in a scientific journal. It is anticipated that clinical and laboratory co-investigators will participate in authorship. The order of authorship and choice of journal will be determined by the PIs and the Sponsor. The data analysis centre for this trial will provide the analyses needed for publication. Information regarding this trial will be posted on ClinicalTrials.gov.

15.4.2 Clinical Trial Registration

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

15.4.3 Clinical Trial Results Disclosure

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

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

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

15.5 Insurance and Compensation for Injury

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

16.0 REFERENCES

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13. Investigator Brochure DENVax Dengue Vaccine (IND 14292), Version 4, 18 March 2013.

Appendix A Responsibilities of the Investigator

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

The investigator agrees to assume the following responsibilities:

1. Conduct the trial in accordance with the protocol.
2. Personally conduct or supervise the staff who will assist in the protocol.
3. Ensure that trial related procedures, including trial specific (non routine/non standard panel) screening assessments are NOT performed on potential subjects, prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the trial are informed of these obligations.
5. Secure prior approval of the trial and any changes by an appropriate IRB/IEC that conform to 21 CFR Part 56, ICH, and local regulatory requirements.
6. Ensure that the IRB/IEC will be responsible for initial review, continuing review, and approval of the protocol. Promptly report to the IRB/IEC all changes in research activity and all anticipated risks to subjects. Make at least yearly reports on the progress of the trial to the IRB/IEC, and issue a final report within 3 months of trial completion.
7. Ensure that requirements for informed consent/informed assent, as outlined in 21 CFR Part 50, ICH and local regulations, are met.
8. Obtain valid informed consent/informed assent from each subject who participates in the trial, and document the date of consent in the subject's medical chart. Valid informed consent/informed assent is the most current version approved by the IRB/IEC. Each informed consent/informed assent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the trial.
9. Prepare and maintain adequate case histories of all persons entered into the trial, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.
11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied vaccines, and return all unused sponsor-supplied vaccines to the sponsor.

12. Report AEs to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.

Appendix B Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (e.g., 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 studies.
- 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 investigator's own country. Investigator acknowledges and consents to the use of his or her personal information by Takeda and other parties for the purposes described above.

Appendix C Elements of the Subject Informed Consent/Informed Assent

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

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

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

the restricted use or disclosure of such information may impact the scientific integrity of the research; and

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

25. Female subjects of childbearing potential (e.g., nonsterilized, premenopausal female subjects) who are sexually active must use adequate contraception (as defined in the informed consent/informed assent) from Month 0 and throughout the duration of the trial. Regular pregnancy tests will be performed throughout the trial for all female subjects of childbearing potential. If a subject is found to be pregnant during trial, no further vaccine doses will be administered and the investigator will offer the subject the choice to receive unblinded treatment information.
26. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.