Title: A Phase II, Double-Blind, Randomized, Controlled Trial to Assess the Safety and Immunogenicity of a Tetravalent Dengue Vaccine with two Different Serotype 2 Potencies in an Adult Population in Singapore.

NCT Number: NCT02425098

Protocol Approve Date: 25 April 2017

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 or company confidential information.

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, Randomized, Controlled Trial to Assess the Safety and Immunogenicity of a Tetravalent Dengue Vaccine with two Different Serotype 2 Potencies in an Adult Population in Singapore.

Safety and Immunogenicity with two Different Serotype 2 Potencies of TDV in Adults

Sponsor:	Takeda Vaccines, Inc. 75 Sidney Street, Cambridge, MA 02139, USA		
Trial Identifier:	DEN-205		
IND Number:	Not Applicable	**EudraCT Number:**	Not Applicable
Vaccine Name:	Tetravalent Dengue Vaccine Candidate (TDV)		
Date:	25 April 2017		
Version:	Version 3.0		

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

Table 1.a Contact Information

Issue	Contact
Serious adverse event and pregnancy reporting	PPD
Responsible Medical Officer (Carries overall responsibility for the conduct of the trial)	PPD

1.2 Approval

REPRESENTATIVES OF TAKEDA

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

- The ethical principles that have their origin in the Declaration of Helsinki
- International 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

{See appended signature page}
PPD
Date

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PPD
Date

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PPD
Date

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 wellbeing 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 10.4 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Appendix A – Responsibilities of the Investigator.

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

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State)

Location of Facility (Country)

1.3 Protocol Amendment No. 2 Summary of Changes

This document describes the changes in reference to the Protocol incorporating Amendment No. 2.

The primary purpose of this amendment is to remove the planned Day 180 (Month 6) interim analysis and to add to the Day 365 (Month 12) visit the recording of receipt of any licensed dengue vaccine.

The rationale for removing the interim analysis initially planned only to support the planning and execution of other trials in the development plan of TDV is that this is no longer necessary. The rationale for recording at the Day 365 (Month 12) visit the receipt of any licensed dengue vaccine is that a licensed dengue vaccine became available in Singapore during the trial conduct and this information is needed to interpret the immune response data.

Full details of the changes are given below.

1.3.1 Amendment History

Date	Amendment Number	Amendment Type	Region
25 January 2015	Initial Protocol	Not applicable	Global
23 March 2015	1	Substantial	Global
25 April 2017	2	Non-substantial	Global

1.3.2 Summary of Changes

Amendment to Protocol Version 2.0, 23 March 2015

Rationale for the Amendment:

Removal of Day 180 (Month 6) interim analysis as no longer necessary and addition of recording at the Day 365 (Month 12) visit of the receipt of any licensed dengue vaccine since a licensed dengue vaccine became available in Singapore during the trial conduct.

Section	Description of change
Title page	Update of the address of the Sponsor
1.2	Update of Clinical Project Management, Pharmacovigilance and Statistics signatories.
2.0	Change to indicate the new availability of a licensed dengue vaccine (at the time of protocol writing no dengue vaccine was available). Change to indicate that no interim analysis will be performed.
2.1	Addition that receipt of any dose of any licensed dengue vaccine throughout the trial should be recorded at Day 365 (Month 12) visit.
4.1	Change to indicate the new availability of a licensed dengue vaccine (at the time of protocol writing no dengue vaccine was available).

Section	Description of change
6.1	Changes to Figure 6-b to indicate the removal of the Day 180 interim analysis.
9.1.2, 9.3.4	Addition that receipt of any dose of any licensed dengue vaccine throughout the trial should be recorded at Day 365 (month 12) visit using the concomitant medication page of the eCRF.
13.1	Removal of planned interim analysis and update of standard text.
13.2	Removal of planned interim analysis and clarification that no interim analysis will be performed.

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2.0 TRIAL SUMMARY

Name of Sponsor: Takeda Vaccines, Inc.		**Product Name:** Tetravalent Dengue Vaccine Candidate (TDV)
Trial Title: A Phase II, Double-Blind, Randomized, Controlled Trial to Assess the Safety and Immunogenicity of a Tetravalent Dengue Vaccine with two Different Serotype 2 Potencies in an Adult Population in Singapore.		
IND No.: Not Applicable		**EudraCT No.:** Not Applicable
Trial Identifier: DEN-205	**Phase:** II	**Trial Blinding Scheme:** Double-Blind

Background

Dengue fever is caused by infection with the dengue virus (DENV), a ribonucleic acid (RNA) virus that occurs as 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 of the following manifestations: headache, retro-orbital pain, myalgia, arthralgia, rash, hemorrhagic manifestations, or leucopenia, and occurrence at the same location and time as other confirmed cases of dengue fever. The most severe forms of dengue infection – DHF and dengue shock syndrome (DSS) – are life threatening. Primary infection with any one of the four dengue serotypes is thought to result in life-long protection from re-infection by the same serotype, but does not protect against a secondary infection by one of the other three dengue serotypes and may lead to an increased risk of severe disease (DHF/DSS).

Treatment of dengue fever is based solely on signs and symptoms, with fluid replacement required for hemorrhagic or shock cases. An antiviral therapy for dengue virus infection is not available. Preventive measures that rely on mosquito control and individual protection are of limited efficacy, complex to implement and questionable in terms of cost-effectiveness. There is a great unmet global public health need for a safe and effective vaccine to reduce the morbidity and mortality associated with dengue disease. Vaccine development has focused on tetravalent vaccines that provide protection against all 4 dengue serotypes simultaneously since all 4 dengue serotypes commonly co-circulate in endemic areas. A first tetravalent dengue vaccine (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 below 9 years of age with the approved vaccine. Additionally, vaccine efficacy was different between serotypes and depended on dengue pre-exposure status. Hence, there is a continued unmet public health need for safer and more efficacious dengue vaccines.

Tetravalent Dengue Vaccine Candidate (TDV) Background:

TDV consists of four 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, DENV-2 Primary Dog Kidney (PDK)-53, originally isolated at Mahidol University, Bangkok, Thailand. The chimeric, attenuated vaccine strains for dengue serotypes 1, 3 and 4 were engineered by replacing the DENV-2 structural genes, pre-membrane (prM) and envelope (E), with the prM and E genes of the wild type (DENV) virus strains, DENV-1 16007, DENV-3 16562 or DENV-4 1036 virus, respectively. TDV is thus comprised of four dengue virus strains: a molecularly characterized, attenuated DENV-2 strain (TDV-2), a DENV-2/1 chimera (TDV-1), a DENV-2/3 chimera (TDV-3) and a DENV-2/4 chimera (TDV-4).

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

Data from three Phase I trials (DEN-101, DEN-102, and DEN-104) and a Phase II trial (DEN-203) have shown satisfactory reactogenicity, safety and immunogenicity profiles of Takeda's TDV in adults in non-endemic areas as well as in adults and children in endemic areas in Asia and Latin America. Currently ongoing and planned Phase II

trials have enabled the selection of a final TDV dose formulation for use in the pivotal program, and results from an ongoing Phase II trial will enable the use of a reconstituted lyophilized formulation.

The current TDV Investigator Brochure contains additional product information and a more detailed review of pre-clinical and clinical studies.

Rationale:

Different formulations of TDV have been previously evaluated in dengue naïve adults in three Phase I trials (DEN-101, -102, and -104). One of these formulations, referred to as High Dose or HD-TDV, has also been evaluated in children and adolescents in a Phase II trial in dengue endemic countries (DEN-203).While these trials have demonstrated that HD-TDV is immunogenic and has an acceptable safety profile, they have also shown that immune responses to the TDV-2 component are consistently and significantly higher than for other serotypes. In addition, vaccine viremia following HD-TDV administration was most commonly associated with TDV-2, suggesting a greater potential for TDV-2 to replicate. This replication may theoretically inhibit replication of the other serotypes, interfering with the immune response. As a result of these observations, Takeda has developed a new formulation, referred to as TDV, CCI [redacted] This new formulation is currently being evaluated in 1800 healthy children aged 2 to <18 years living in dengue endemic countries in the DEN 204 trial.

Trial DEN-205 will compare the immune response to the new TDV formulation with HD-TDV, in dengue naïve and previously exposed subjects. Adult subjects will be enrolled in Singapore because the semi-endemic dengue epidemiology in this country enables the enrolment of subjects who are either naïve or pre-exposed to dengue. Furthermore, the blood volumes and sample management required to characterize cellular immune responses to TDV are limiting factors in pediatric studies in dengue endemic countries. Enrolling adult subjects in Singapore enables the investigation of cell-mediated immunity (CMI).

In order to ensure the enrolment of dengue naïve and previously exposed subjects, screening with a local dengue IgG indirect enzyme-linked immunosorbent assay (ELISA) will be performed prior to randomization. The IgG status at baseline will provide a rapid indication of previous exposure to dengue, enabling stratification of randomization. The analysis of the trial endpoints by baseline dengue seropositivity will however be based on the microneutralization test (MNT) result of blood samples taken on the day of vaccination and tested at a central laboratory, to ensure consistent assessments across the program.

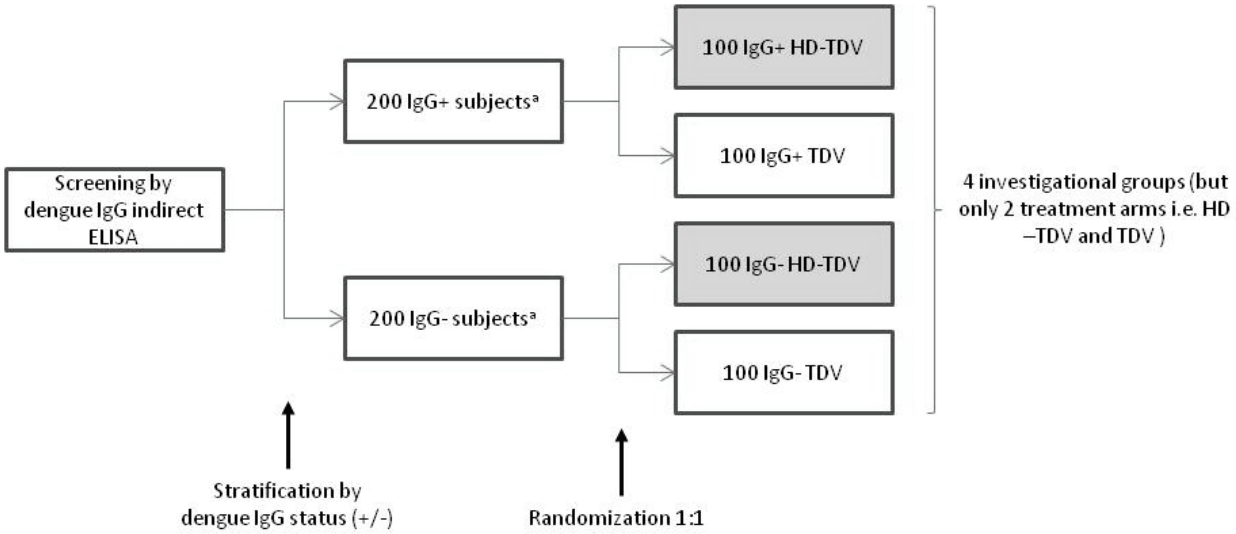
Trial Design:

This is a descriptive Phase II, double-blind, randomized, and controlled trial in 400 subjects aged 21 to 45 years living in Singapore. Subjects will be randomized (1:1) into two treatment arms:

- Arm 1 will receive one subcutaneous (SC) dose of HD-TDV;
- Arm 2 will receive one SC dose of TDV.

Randomization will be stratified based on the dengue IgG status (positive (+) or negative (-)) at screening, resulting in four investigational groups (Figure 2.a).

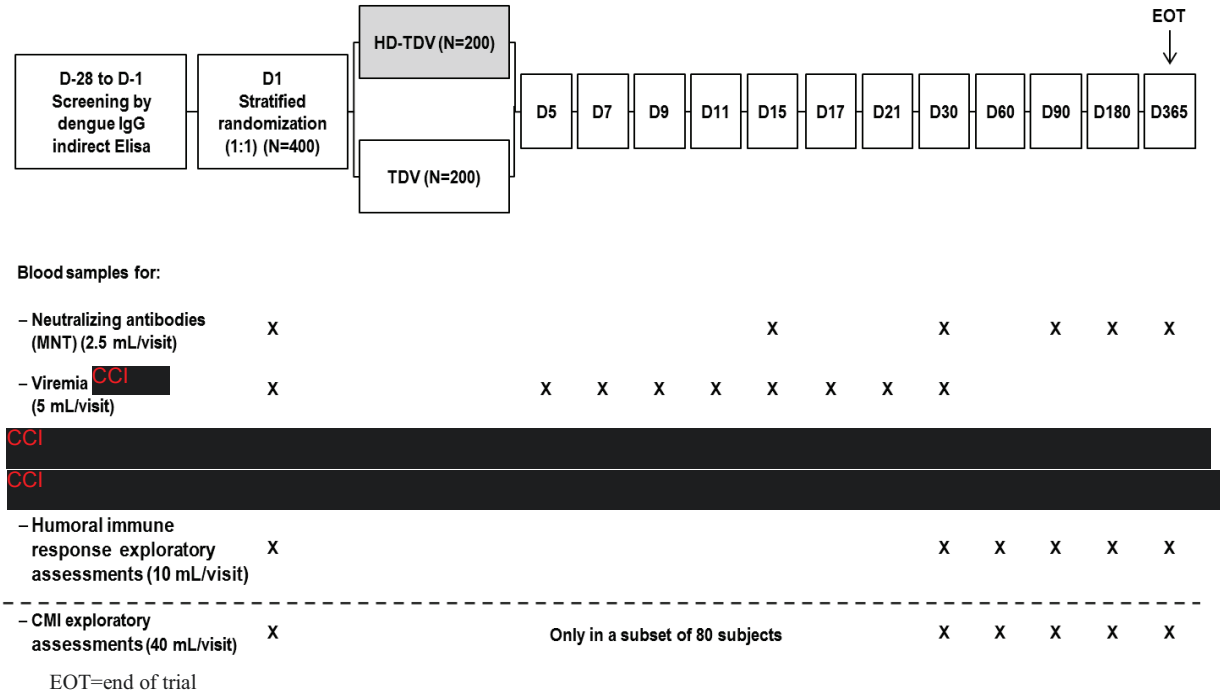
Figure 2.a Den-205 schematic showing the stratified randomization process



[a]Approximately 40 subjects in each of the IgG positive and negative groups will form the CMI subset.

Subjects will be followed for one year, with 13 scheduled visits, for the assessment of reactogenicity, safety and/or immunogenicity (Figure 2.b). Cell-mediated immunity will be assessed in a subset of approximately 80 subjects (approximately 40 subjects in each of the IgG positive and negative groups). This CMI subset will consist of volunteers identified at the time of randomization.

Figure 2.b Den-205 schematic showing subject flow through the trial



EOT=end of trial

Immunogenicity evaluation:

- Neutralizing antibodies (MNT) will be measured on blood samples collected pre-vaccination on Day 1 (Month 0) and post-vaccination on Days 15, 30 (Month 1), 90 (Month 3), 180 (Month 6) and 365 (Month 12).

Assessment of viral replication:

- Vaccine viremia will be assessed on blood samples collected pre-vaccination on Day 1 (Month 0) and post-vaccination on Days 5, 7, 9, 11, 15, 17, 21 and 30 (Month 1).

Safety evaluation:

- Subjects will be provided with a diary card for the recording of:
  - Solicited local adverse events (AEs) for 7 days following vaccination (day of vaccination + 6 days). These will include: 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: fever, headache, asthenia, malaise, and myalgia.
  - Unsolicited AEs for 28 days following vaccination (day of vaccination + 27 subsequent days).
- Serious adverse events (SAEs) throughout the trial.

Exploratory assessments:

- CCI [redacted]
- Neutralizing and non-neutralizing antibodies will be characterized on blood samples collected pre-vaccination on Day 1 (Month 0), and post-vaccination on Days 30 (Month 1), 60 (Month 2), 90 (Month 3), 180 (Month 6) and 365 (Month 12) by different exploratory assays.
- Cell-mediated immunity will be assessed in a subset of subjects on blood samples collected pre-vaccination on Day 1 (Month 0), and post-vaccination on Days 30 (Month 1), 60 (Month 2), 90 (Month 3), 180 (Month 6) and 365 (Month 12).

Primary Objective:

- To assess the post-vaccination neutralizing antibody response against each dengue serotype by treatment arm.

Secondary Objectives:

Safety

- To assess the safety of HD-TDV and TDV by treatment arm and baseline dengue seropositivity (MNT).

Immunogenicity

- To assess the post-vaccination neutralizing antibody response against each dengue serotype by treatment arm and baseline dengue seropositivity (MNT).

Vaccine Viremia

- To assess vaccine viremia post-vaccination by treatment arm and baseline dengue seropositivity (MNT).

Note: Baseline dengue seropositivity (MNT) is defined as a reciprocal neutralizing titer ≥10 for one or more dengue serotype at baseline.

Exploratory Objectives:

- CCI [redacted]

CCI [redacted]

- To characterize humoral immune response.
- To characterize cell-mediated immunity in the CMI subset.

Subject Population:

Healthy subjects: yes

Planned minimum/ maximum Age: 21 / 45 years

Planned number of subjects: 400

Planned number of arms: Two treatment arms in a 1:1 ratio (HD-TDV: 200 subjects; TDV: 200 subjects), single SC vaccination on Day 1 (Month 0).

Criteria for Inclusion:

1. The subject signs and dates a written informed consent form where applicable, and any required privacy authorization prior to the initiation of any trial procedures, after the nature of the trial has been explained according to local regulatory requirements.
2. The subject is aged 21 to 45 years of age, inclusive.
3. 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.
4. Individuals who can comply with trial procedures and are available for the duration of follow-up.
5. Subjects have self-declared as never having been vaccinated against Yellow Fever or Japanese Encephalitis Virus.

Criteria for Exclusion:

1. Febrile illness (temperature ≥38°C or ≥100.4°F) or moderate or severe acute illness or infection at the time of enrollment.
2. History or any illness that, in the opinion of the Investigator, might interfere with the results of the trial or pose an additional risk to the subject due to participation in the trial, including but not limited to:
    a. Known hypersensitivity or allergy to any of the vaccine components.
    b. Female subjects 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 (Month 0) (use of inhaled, intranasal, or topical corticosteroids is allowed).
        ii. Receipt of parenteral steroids (equivalent to 20 mg/day prednisone ≥12 weeks/≥ 2 mg/kg body weight/day prednisone ≥2 weeks) within 60 days prior to Day 1 (Month 0).
        iii. Administration of immunoglobulins and/or any blood products within the 3 months prior to Day 1 (Month 0) or planned administration during the trial.
        iv. Receipt of immunostimulants within 60 days prior to Day 1 (Month 0).
        v. Immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy within 6 months prior to Day 1 (Month 0).
        vi. Human immunodeficiency virus (HIV) infection or HIV-related disease.
        vii. Hepatitis C virus (HCV) infection.
        viii. Genetic immunodeficiency.

3. Receipt of any other vaccine within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to Day 1 (Month 0) or planning to receive any vaccine within 28 days after Day 1 (Month 0).
4. Participation in any clinical trial with another investigational product 30 days prior to Day 1 (Month 0) or intent to participate in another clinical trial at any time during the conduct of this trial.
5. Previous participation in any clinical trial of a dengue candidate vaccine, or previous receipt of a dengue vaccine.
6. First-degree relatives of individuals involved in trial conduct.
7. For females of childbearing potential[1] who are sexually active, and who have not used any of the acceptable contraceptive method[2] for at least 2 months prior to Day 1 (Month 0).
8. Females of childbearing potential who are sexually active, and who refuse to use an acceptable contraceptive method from signing the informed consent to up to 6 weeks post-vaccination.

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 Vaccines:

TDV is a tetravalent dengue vaccine comprised of four dengue virus strains. Two TDV formulations will be evaluated in this trial:

- HD-TDV: [redacted] CCI [redacted].
- TDV: [redacted] CCI [redacted]

Duration of the Trial:	**Period of Evaluation:**
For each subject, approximately 365 days (12 months) following vaccination on Day 1 (Month 0).	For the duration of a subject's participation.

Main Criteria for Evaluation and Assessments:

Primary endpoints:

- Geometric mean titers (GMTs) of neutralizing antibodies for each of the four dengue serotypes post-vaccination on Days 15, 30 (Month 1), 90 (Month 3), 180 (Month 6), 365 (Month 12).
- Seropositivity rates (% of subjects) for each of the four dengue serotypes post-vaccination on Days 15, 30 (Month 1), 90 (Month 3), 180 (Month 6), 365 (Month 12) where seropositivity is defined as a reciprocal neutralizing titer ≥10.

[1] Defined as status post onset of menarche and not meeting any of the following conditions: bilateral tubal ligation (at least 1 year previously), bilateral oophorectomy (at least 1 year previously) or hysterectomy.
[2] Acceptable birth control methods are defined as one or more of the following: hormonal contraceptive (such as oral, injection, transdermal patch, implant, cervical ring); barrier (condom with spermicide or diaphragm with spermicide) each and every time during intercourse; intrauterine device (IUD); monogamous relationship with vasectomized partner (partner must have been vasectomized for at least 6 months prior to Day 1 [Month 0]).

Secondary endpoints:

Safety

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

Immunogenicity

- Refer to primary endpoints, but will be analyzed by dengue baseline seropositivity (MNT).

Vaccine Viremia

- Incidence, duration, and level of vaccine viremia for each of the four dengue serotypes post-vaccination.

Exploratory endpoints:

- CCI [redacted].
- Additional analyses will be performed to characterize humoral immune response (all subjects) and CMI response (CMI subset).

Statistical considerations:

All analyses will be descriptive; no statistical hypotheses will be tested in this trial.

Analysis Sets

Safety Set: The Safety Set will consist of all randomized subjects who received the trial vaccine.

Full Analysis Set (FAS): The FAS will consist of all randomized subjects who received the trial vaccination and for whom valid a pre-dose and at least one valid post-dose blood sample is taken.

Per-Protocol Set (PPS): The PPS will consist of subjects in the FAS who have no major protocol violations. The major protocol violation criteria will be defined as part of the blinded data review prior to the unblinding of subject's 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.

The primary analysis of immunogenicity and vaccine viremia endpoints will be based on the PPS; other supportive analysis may be provided for the FAS. The safety analysis will be based on the Safety Set.

Demographics and other baseline characteristics

Age, gender, race, and other baseline characteristics will be summarized descriptively by treatment arm and baseline dengue seropositivity (MNT) for all randomized subjects.

Immunogenicity Analysis

For primary and secondary immunogenicity endpoints i.e. GMTs of neutralizing antibodies and seropositivity rates [%] for each of the four dengue serotypes, descriptive statistics and 95% confidence intervals (CIs) will be provided by treatment arm (overall), and by treatment arm and baseline dengue seropositivity (MNT) for each applicable visit. CMI data will be summarized descriptively. Seropositivity is defined as a reciprocal neutralizing titer ≥10.

Vaccine Viremia Analysis

For vaccine viremia endpoints (i.e., incidence, duration and level of vaccine viremia for each of the four dengue serotypes after vaccination) descriptive statistics and 95% CIs will be provided by treatment arm and dengue baseline seropositivity (MNT) for each applicable visit.

Safety Analysis

All summaries of safety data will be performed using the Safety Set. The safety data will be summarized by treatment arm. For some key tables, the safety data will also be summarized by treatment arm and dengue baseline seropositivity (MNT). Full details will be provided in the Statistical Analysis Plan (SAP).

Solicited AEs

Solicited local AEs and solicited systemic AEs will be assessed by the use of diary cards for 7 days and 14 days, respectively, following vaccination (vaccination day included).

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 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 subjects with more than 1 episode of the same event, the maximum severity will be used for tabulations.

Unsolicited AEs

Unsolicited AEs will be assessed by the use of diary cards for 28 days following vaccination (vaccination day included).

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). AEs leading to withdrawal will also be summarized.

All unsolicited AEs up to 28 days after 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 post-vaccination, 2) with onset between 1 and 14 days post-vaccination, and 3) with onset between 15 and 28 days post-vaccination.

Note: Baseline dengue seropositivity (MNT) is defined as a reciprocal neutralizing titer $\geq$10 for one or more dengue serotype at baseline.

Sample size justification:

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

Interim analysis:

No interim analysis will be performed.

Data Monitoring Committee:

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

DEN-205 Version 3.0 (25 April 2017)

2.1 Schedule of Trial Procedures

Table 2.a Schedule of Trial Procedures

Visits		1	2	3	4	5	6	7	8	9	10	11	12	13 EOT[a]
Day (Month)	Screening	D1 (Month 0)	D5	D7	D9	D11	D15	D17	D21	D30 (Month 1)	D60 (Month 2)	D90 (Month 3)	D180 (Month 6)	D365 (Month 12)
Time window	-28 to -1 days		±0 days	±1 day	±1 day	±1 day	±1 day	±1 day	±2 days	+4 days	±5 days	±5 days	±10 days	±15 days
Signed Informed Consent [b]	X													
Assessment of Eligibility Criteria [c]	X	X												
Demographics	X													
Medical History	X													
Concomitant medication [d]	X	X												X
Complete physical examination[e]	X													
Targeted physical examination [f]		X												X
Symptom-directed physical examination [g]			X	X	X	X	X	X	X	X	X	X	X	
Vital Signs [h]	X				X			X		X				
Pregnancy test [i]	X	X												
Screening results		X												
Randomization		X												

Visits		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13 EOT[a]**
Day (Month)	Screening	D1 (Month 0)	D5	D7	D9	D11	D15	D17	D21	D30 (Month 1)	D60 (Month 2)	D90 (Month 3)	D180 (Month 6)	D365 (Month 12)
Time window	-28 to -1 days		±0 days	±1 day	±1 day	±1 day	±1 day	±1 day	±2 days	+4 days	±5 days	±5 days	±10 days	±15 days
Vaccine administration		X												
Injection Site Evaluation [j]		X		X										
Diary card distribution [k]		X												
Diary card collection and review				X			X			X				
Serious Adverse Events (SAEs) [l]		X	X	X	X	X	X	X	X	X	X	X	X	X
Blood Collection [m]														
Blood sample for screening dengue IgG indirect ELISA (2.5 mL)	X													
Blood sample for dengue MNT (2.5 mL)		X					X			X		X	X	X
CCI [redacted]														

Visits		**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13 EOT[a]**
Day (Month)	Screening	D1 (Month 0)	D5	D7	D9	D11	D15	D17	D21	D30 (Month 1)	D60 (Month 2)	D90 (Month 3)	D180 (Month 6)	D365 (Month 12)
Time window	-28 to -1 days		±0 days	±1 day	±1 day	±1 day	±1 day	±1 day	±2 days	+4 days	±5 days	±5 days	±10 days	±15 days
CCI														
CCI														
Blood sample for vaccine viremia (2.5 mL)		X	X	X	X	X	X	X	X	X				
Blood sample for humoral immune response (10 mL)		X								X	X	X	X	X
Blood sample for cell-mediated immunity (40 mL)[o]		X								X	X	X	X	X

Notes: ELISA=enzyme-linked immunosorbent assay; EOT=End Of Trial; Ig=immunoglobulin; MNT=microneutralization test; CCI

Footnotes:

(a) End of the Trial (EOT) is Day 365 (Month 12), which corresponds to 365 days following vaccination. If the subject terminates early, Day 365 procedures should be performed.
(b) The signed informed consent of the subject needs to be obtained before performing any other trial procedure.
(c) Eligibility by review of inclusion/exclusion criteria will be documented at screening and may be re-assessed before randomization on Day 1 (Month 0).
(d) Concomitant therapy (all medications) and vaccine history from 4 weeks prior to TDV vaccination will be collected on Day 1 (Month 0) and Day 365 (Month 12).Receipt of any dose of any licensed dengue vaccine throughout the trial.
(e) Physical examination including measurement of weight and height; body mass index (BMI) will be calculated automatically.
(f) Including (but not limited to) the measurement of vital signs.
(g) Symptom-directed examinations should assess clinically significant changes from the baseline examination.

(h) These will include (but are not limited to) systolic blood pressure/diastolic blood pressure, heart rate and temperature.
(i) In women of childbearing potential, urine pregnancy tests will be performed after informed consent is obtained at screening and before vaccination on Day 1 (Month 0) (within one day prior).
(j) Injection site evaluation (pain, erythema and swelling) at 30 minutes after vaccination on Day 1(Month 0) and on Day 7.
(k) Diary cards will be distributed for the collection of:
    a. Solicited local AEs until Day 7 (day of vaccination + 6 subsequent days),
    b. Solicited systemic AEs until Day 14 (day of vaccination + 13 subsequent days), and
    c. Unsolicited AEs until Day 28 (day of vaccination and + 27 subsequent days).
(l) SAEs will be reported to the Sponsor within 24 hours of the Investigator becoming aware of the event.
(m) Blood samples on Day 1 (Month 0) need to be collected **before vaccination**.
(n) Blood collection at screening is used to determine dengue baseline immune status (i.e., dengue naïve and pre-exposed subjects).
(o) Cell-mediated immunity (CMI) will be assessed in a subset of subjects, referred to as the CMI subset.

3.0 TRIAL REFERENCE INFORMATION

3.1 Trial-Related Responsibilities

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

3.2 Principal Investigator/Coordinating Investigator

The Sponsor will select a Signatory 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 study report and by doing so agrees that it accurately describes the results of the trial.

3.3 List of Abbreviations

AE	Adverse Event
BMI	Body Mass Index
CMI	Cell-mediated Immunity
DEN	Dengue Virus
DENV	Dengue Virus (wild type)
DHF	Dengue Hemorrhagic Fever
DSS	Dengue Shock Syndrome
E	Envelope
ELISA	Enzyme-linked immunosorbent assay
eCRF	electronic Case Report Form
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMT	Geometric Mean Titer
HD-TDV	High dose TDV formulation
HCV	Hepatitis C Virus
HIV	Human immunodeficiency virus
IB	Investigator Brochure
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
Ig	Immunoglobulin
Inc	Incorporated
IRB	Institutional Review Board
IUD	Intrauterine device
IWRS	Interactive Web Response System
MedDRA	Medical Dictionary for Regulatory Activities
MNT	Microneutralization test
CCI	[redacted]
PBMC(s)	Peripheral Blood Mononuclear Cells
PFU	Plaque Forming Units
PPS	Per Protocol Set
prM	pre-membrane
PT	Preferred term

RNA	Ribonucleic Acid
SAE	Serious Adverse Event
SC	Subcutaneous
SOC	System Organ Class
SOP	Standard operating procedures
SUSAR	Suspected Unexpected Serious Adverse Reaction
TDV	Tetravalent Dengue Vaccine Candidate
US	United States
WHO	World Health Organization

3.4 Corporate Identification

TV Takeda Vaccines, Inc.

4.0 INTRODUCTION

4.1 Background

Dengue fever is caused by infection with the dengue virus (DENV), a ribonucleic acid (RNA) virus that occurs as 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 of the following manifestations: headache, retro-orbital pain, myalgia, arthralgia, rash, hemorrhagic manifestations, or leucopenia, and occurrence at the same location and time as other confirmed cases of dengue fever. The most severe forms of dengue infection – DHF and dengue shock syndrome (DSS) – are life threatening. Primary infection with any one of the four dengue serotypes is thought to result in life-long protection from re-infection by the same serotype, but does not protect against a secondary infection by one of the other three dengue serotypes and may lead to an increased risk of severe disease (DHF/DSS) [3-6].

Treatment of dengue fever is based solely on signs and symptoms, with fluid replacement required for hemorrhagic or shock cases. An antiviral therapy for dengue virus infection is not available. Preventive measures that rely on mosquito control and individual protection are of limited efficacy, complex to implement and questionable in terms of cost-effectiveness. There is a great unmet global public health need for a safe and effective vaccine to reduce the morbidity and mortality associated with dengue disease [1-7]. Vaccine development has focused on tetravalent vaccines that provide protection against all 4 dengue serotypes simultaneously since all 4 dengue serotypes commonly co-circulate in endemic areas. A first tetravalent dengue vaccine (CYD-TDV) has been recently approved in some countries in Asia and Latin America. However, the initial findings suggest an unfavorable risk-benefit profile for younger subjects below 9 years of age with the approved vaccine. Additionally, vaccine efficacy was different between serotypes and depended on dengue pre-exposure status. Hence, there is a continued unmet public health need for safer and more efficacious dengue vaccines.

TDV Background:

TDV consists of four 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 [8]. 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 (DENV) virus strains, DENV-1 16007, DENV-3 16562 or DENV-4 1036 virus, respectively [9]. TDV is thus comprised of four dengue

virus strains: a molecularly characterized, attenuated DENV-2 strain (TDV-2), a DENV-2/1 chimera (TDV-1), a DENV-2/3 chimera (TDV-3) and a DENV-2/4 chimera (TDV-4).

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

Data from three Phase I trial (DEN-101, DEN-102, and DEN-104) and a Phase II trial (DEN-203) have shown satisfactory reactogenicity, safety and immunogenicity profiles of Takeda's TDV in adults in non-endemic areas as well as in adults and children in endemic areas in Asia and Latin America. Currently ongoing and planned Phase II trials have enabled the selection of a final TDV dose formulation for use in the pivotal program, and results from an ongoing Phase II trial will enable the use of a reconstituted lyophilized formulation.

In the current Investigator Brochure (IB) of TDV additional product information and a more detailed review of pre-clinical and clinical studies is provided [10].

4.2 Rationale for the Proposed Trial

Different formulations of TDV have been previously evaluated in dengue naïve adults in three Phase I trials (DEN-101, -102, and -104). One of these formulations, referred to as High Dose or HD-TDV, has also been evaluated in children and adolescents in a Phase II trial in dengue endemic countries (DEN-203). While these trials have demonstrated that HD-TDV is immunogenic and has an acceptable safety profile, they have also shown that immune responses to the TDV-2 component are consistently and significantly higher than for other serotypes. In addition, vaccine viremia following HD-TDV administration was most commonly associated with TDV-2, suggesting a greater potential for TDV-2 to replicate. This replication may theoretically inhibit replication of the other serotypes, interfering with the immune response. As a result of these observations, Takeda has developed a new formulation, referred to as TDV, CCI [redacted] This new formulation is currently being evaluated in 1800 healthy children aged 2 to <18 years living in dengue endemic countries in the DEN 204 trial.

Trial DEN-205 will compare the immune response to the new TDV formulation with HD-TDV, in dengue naïve and previously exposed subjects. Adult subjects will be enrolled in Singapore because the semi-endemic dengue epidemiology in this country enables the enrolment of subjects who are either naïve or pre-exposed to dengue [11]. Furthermore, the blood volumes and sample management required to characterize cellular immune responses to TDV are limiting factors in pediatric studies in dengue endemic countries. Enrolling adult subjects in Singapore enables the investigation of cellular mediated immunity (CMI).

In order to ensure the enrolment of dengue naïve and previously exposed subjects, screening with a local dengue IgG indirect enzyme-linked immunosorbent assay (ELISA) will be performed prior to randomization. The IgG status at baseline will provide a rapid indication of previous exposure to dengue, enabling stratification of randomization. The analysis of the trial endpoints by baseline dengue seropositivity will however be based on the microneutralization test (MNT) result of blood

samples taken on the day of vaccination and tested at a central laboratory, to ensure consistent assessments across the program.

The trial will be conducted in accordance with the protocol, the International Conference on Harmonization and Good Clinical Practice (ICH-GCP) Guidelines and any applicable regulatory requirements.

5.0 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

- To assess the post-vaccination neutralizing antibody response against each dengue serotype by treatment arm.

5.1.2 Secondary Objectives

Safety

- To assess the safety of HD-TDV and TDV by treatment arm and baseline dengue seropositivity (MNT).

Immunogenicity

- To assess the post-vaccination neutralizing antibody response against each dengue serotype by treatment arm and baseline dengue seropositivity (MNT).

Vaccine viremia

- To assess vaccine viremia post-vaccination by treatment arm and baseline dengue seropositivity (MNT).

Note: Baseline dengue seropositivity (MNT) is defined as a reciprocal neutralizing titer ≥10 for one or more dengue serotype at baseline.

5.1.3 Exploratory Objectives

- CCI [redacted]
- To characterize humoral immune responses.
- To characterize cell-mediated immunity (CMI) in the CMI subset.

5.2 Endpoints

5.2.1 Primary Endpoints

- Geometric mean titers (GMTs) of neutralizing antibodies for each of the four dengue serotypes post-vaccination on Days 15, 30 (Month 1), 90 (Month 3), 180 (Month 6), 365 (Month 12).
- Seropositivity rates (% of subjects) for each of the four dengue serotypes post-vaccination on Days 15, 30 (Month 1), 90 (Month 3), 180 (Month 6), 365 (Month 12) where seropositivity is defined as a reciprocal neutralizing titer ≥10.

5.2.2 Secondary Endpoints

Safety

- Frequency and severity of solicited local (injection site) adverse events (AEs) for 7 days and solicited systemic AEs for 14 days after vaccination.
- Percentage of subjects with any unsolicited AEs for 28 days after vaccination.
- Percentage of subjects with serious adverse events (SAEs) throughout the trial.

Immunogenicity

- Refer to primary endpoints, but will be analyzed by dengue baseline seropositivity (MNT).

Vaccine viremia

- Incidence, duration, and level of vaccine viremia for each of the four dengue serotypes post-vaccination.

5.2.3 Exploratory Endpoints

- CCI [redacted]
- Additional analyses will be performed to characterize humoral immune response (all subjects) and cell-mediated immune response (CMI subset).

6.0 TRIAL DESIGN AND DESCRIPTION

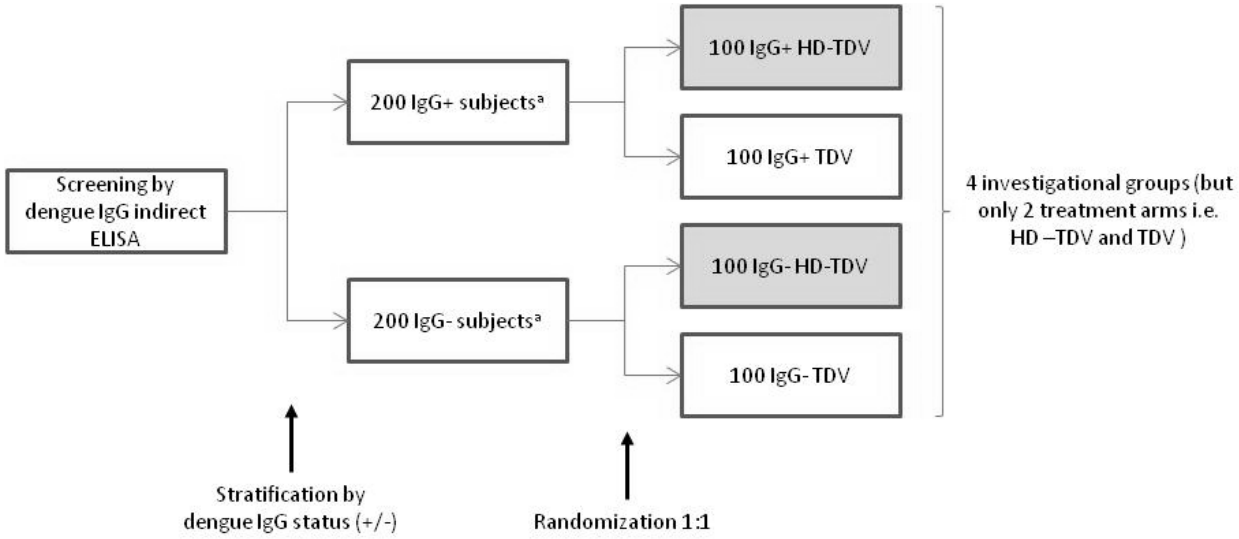
6.1 Trial Design

This is a descriptive, Phase II, double-blind, randomized, and controlled trial in 400 subjects aged 21 to 45 years living in Singapore. Subjects will be randomized (1:1) into two treatment arms:

- Arm 1 will receive one subcutaneous (SC) dose of HD-TDV;
- Arm 2 will receive one SC dose of TDV.

Randomization will be stratified based on the dengue IgG status (positive / negative) at screening, resulting in four investigational groups (Figure 6.a).

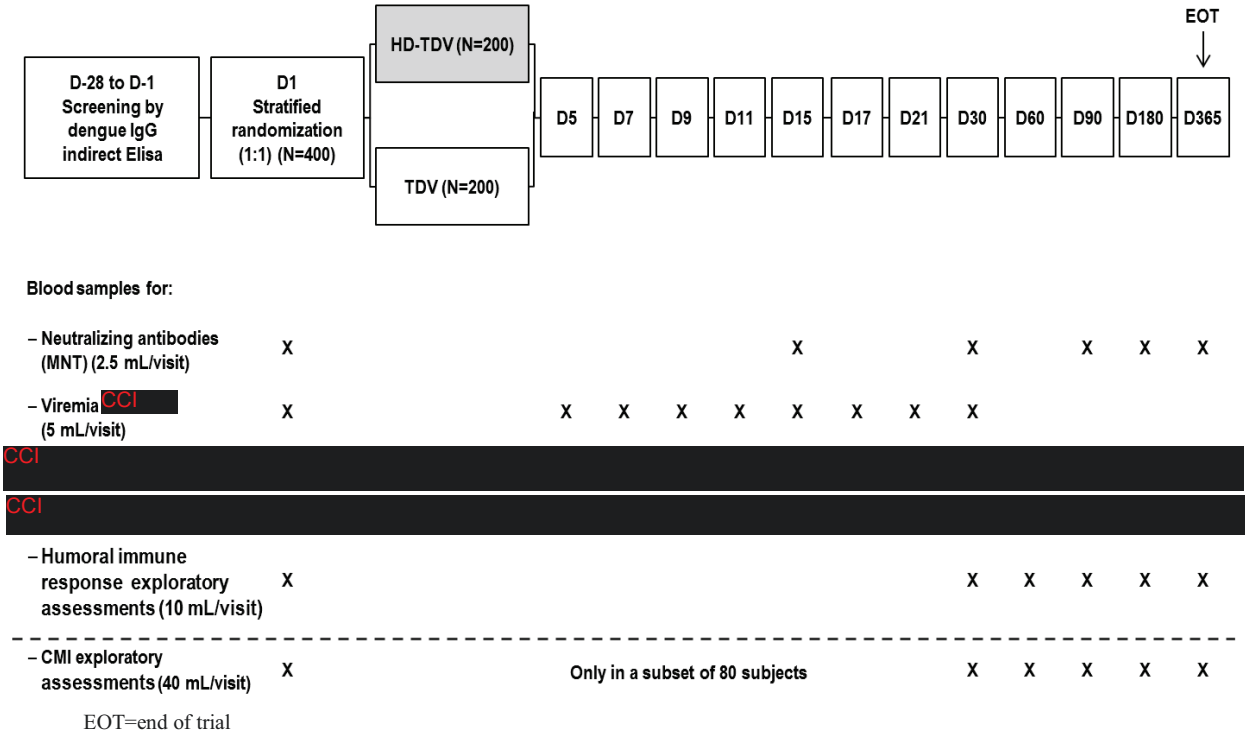
Figure 6.a Den-205 schematic showing the stratified randomization process



[a]Approximately 40 subjects in each of the IgG positive and negative groups will form the CMI subset.

Subjects will be followed for one year, with 13 scheduled visits, for the assessment of reactogenicity, safety and/or immunogenicity (Figure 6.b). Cell-mediated immunity will be assessed in a subset of approximately 80 subjects (approximately 40 subjects in each of the IgG positive and negative groups). This CMI subset will consist of volunteers identified at the time of randomization.

Figure 6.b DEN-205 schematic showing subject flow through the trial



EOT=end of trial

Immunogenicity evaluation:

- Neutralizing antibodies (MNT) will be measured on blood samples collected pre-vaccination on Day 1 (Month 0) and post-vaccination on Days 15, 30 (Month 1), 90 (Month 3), 180 (Month 6) and 365 (Month 12).

Assessment of viral replication:

- Vaccine viremia will be assessed on blood samples collected pre-vaccination on Day 1 (Month 0) and post-vaccination on Days 5, 7, 9, 11, 15, 17, 21 and 30 (Month 1).

Safety evaluation:

- Subjects will be provided with a diary card for the recording of:
  - Solicited local AEs for 7 days following vaccination (day of vaccination + 6 days). These will include: 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: fever, headache, asthenia, malaise, and myalgia.

  - Unsolicited AEs for 28 days following vaccination (day of vaccination + 27 subsequent days).

- Serious adverse events throughout the trial.

Exploratory assessments:

- CCI [redacted]

- Neutralizing and non-neutralizing antibodies will be characterized on blood samples collected pre-vaccination on Day 1 (Month 0), and post-vaccination on Days 30 (Month 1), 60 (Month 2), 90 (Month 3), 180 (Month 6) and 365 (Month 12) by different exploratory assays.
- CMI will be assessed in a subset of subjects on blood samples collected pre-vaccination on Day 1 (Month 0), and post-vaccination on Days 30 (Month 1), 60 (Month 2), 90 (Month 3), 180 (Month 6) and 365 (Month 12).

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.

Data generated to date show substantial increases in GMTs of dengue neutralizing antibodies to all four serotypes after a single dose of HD-TDV, with the highest titers being to DEN 2. There was a limited increase in titer following a second dose given at 3 months after the first. Therefore, a single dose regimen is being evaluated in trial DEN 204 and used in the present trial.

The rationale for a reduced dosage of TDV-2 is based on data from previous Phase I trials with HD-TDV (DEN-101, -102 and -104) which showed a consistently greater immune response and frequency of vaccine viremia for TDV-2 than for the three other dengue vaccine strains, suggesting a greater potential for TDV-2 to replicate. This TDV-2 replication may theoretically inhibit replication of the other serotypes, interfering with the immune response.

Prior dengue infection may influence immune responses elicited by TDV as well as may have an impact on vaccine viremia due to the four dengue vaccine strains. Therefore, the trial will be conducted in a dengue semi-endemic country allowing characterization of humoral immune responses following vaccination with a prophylactic dengue vaccine when given to both dengue

naïve and dengue pre-exposed subjects. In addition, CMI will be characterized in a subset of subjects (approximately 80 subjects), referred to as the CMI subset.

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

The duration of the trial for each subject will be approximately 365 days (12 months) following vaccination on Day 1 (Month 0).

6.4 Premature Termination or Suspension of Trial or Investigational Site

6.4.1 Criteria for Premature Termination or Suspension of the Trial

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

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

6.4.2 Criteria for Premature Termination or Suspension of Investigational Sites

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

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 signs and dates a written informed consent form where applicable, and any required privacy authorization prior to the initiation of any trial procedures, after the nature of the trial has been explained according to local regulatory requirements (Appendix C).
2. The subject is aged 21 to 45 years of age, inclusive.
3. 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.
4. Individuals who can comply with trial procedures and are available for the duration of follow-up.
5. Subjects have self-declared as never having been vaccinated against Yellow Fever or Japanese Encephalitis Virus.

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.
2. History or any illness that, in the opinion of the Investigator, might interfere with the results of the trial or pose an additional risk to the subject due to participation in the trial, including but not limited to:
    a. Known hypersensitivity or allergy to any of the vaccine components.
    b. Female subjects 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 (Month 0) (use of inhaled, intranasal, or topical corticosteroids is allowed).

ii. Receipt of parenteral steroids (equivalent to 20 mg/day prednisone ≥12 weeks/≥ 2 mg/kg body weight/day prednisone ≥2 weeks) within 60 days prior to Day 1 (Month 0).

iii. Administration of immunoglobulins and/or any blood products within the ***3*** months prior to Day 1 (Month 0) or planned administration during the trial.

iv. Receipt of immunostimulants within 60 days prior to Day 1(Month 0).

v. Immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy within 6 months prior to Day 1 (Month 0).

vi. Human immunodeficiency virus (HIV) infection and HIV-related diseases.

vii. Hepatitis C virus (HCV) infection.

viii. Genetic immunodeficiency.

3. Receipt of any other vaccine within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to Day 1 (Month 0) or planning to receive any vaccine within 28 days after Day 1 (Month 0).
4. Participation in any clinical trial with another investigational product 30 days prior to Day 1 (Month 0) or intent to participate in another clinical trial at any time during the conduct of this trial.
5. Previous participation in any clinical trial of a dengue candidate vaccine, or previous receipt of a dengue vaccine.
6. First-degree relatives of individuals involved in trial conduct.
7. For females of childbearing potential who are sexually active, and who have not used any of the acceptable contraceptive methods for at least 2 months prior to Day 1 (Month 0).
    a. Of childbearing potential is defined as status post onset of menarche and not meeting any of the following conditions: bilateral tubal ligation (at least 1 year previously), bilateral oophorectomy (at least 1 year previously) or hysterectomy.
    b. Acceptable birth control methods are defined as 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 Day 1 [Month 0]).

8. Females of childbearing potential who are sexually active, and who refuse to use an acceptable contraceptive method from signing the informed consent up to 6 weeks post-vaccination.

There may be instances when individuals meet all entry criteria except one that relates to transient clinical circumstances (e.g., 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 and/or Blood Sampling

After enrollment, subjects may encounter clinical circumstances that warrant a delay in the administration of 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 clinically significant active infection (as assessed by the Investigator) or temperature >38.0°C (>100.4°F), within 3 days of intended trial vaccination (consider whether applicable as a criterion for delay or as an exclusion criterion). Refer to Section 7.2.
- Individuals who have received blood, blood products and/or plasma derivatives or any parenteral immunoglobulin preparation in the past 3 months. Refer to Section 7.2.
- Individuals who received any other vaccines within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to planned vaccination or blood sampling. Refer to Section 7.2.

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 (eCRF) using the following categories. For screen failure subjects, see also Section 9.1.13.

1. Protocol violation: The subject may remain in the trial unless continuation in the trial jeopardizes the subject's health, safety or rights.
2. AE: The subject has experienced an AE that requires early termination because continued participation imposes an unacceptable risk to the subject's health or the subject is unwilling to continue 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. Study terminated by Sponsor.
6. Pregnancy: Any subject who, despite the requirement for adequate contraception, becomes pregnant during the trial will not receive further trial interventions. 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 at any time during the trial without giving a reason. Should a subject's participation be discontinued, the primary criterion for termination must be recorded. In addition, efforts should be made to perform all procedures as scheduled for the Final Visit. Discontinued or withdrawn subjects will not be replaced.

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

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

8.1 Investigational Vaccines and Materials

The investigational product is TDV, a tetravalent dengue vaccine comprised of four dengue virus strains. Two TDV formulations will be evaluated in this trial:

– HD-TDV: [redacted]

– TDV: [redacted]

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

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

This trial will involve the use of TDV for SC injection. [redacted]

TDV (HD-TDV and TDV) is lyophilized and presented in a labeled, single-use, 2 mL glass vial with a [redacted] rubber stopper and flip-top aluminum over seal that once reconstituted* will contain a single [redacted] liquid dose for SC injection.

[redacted]

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

HD-TDV and TDV vaccines will be provided by the Sponsor in a uniquely numbered carton and will be dispensed in a blinded manner by the Interactive Web Response System (IWRS).

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

8.1.2 Storage

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

All clinical trial material must be kept in an appropriate, limited-access, secure place until it is used or returned to the Sponsor or designee for destruction. All Sponsor-supplied vaccines must be

stored under the conditions specified on the label, and remain in the original container until dispensed. A daily temperature log of the vaccine storage area must be maintained every working day.

8.1.3 Dose and Regimen

Subjects will receive on Day 1 (Month 0) either one dose of HD-TDV or TDV according to their random assignment.

8.2 Investigational Vaccine Assignment and Dispensing Procedures

The Investigator or designee will access the IWRS to obtain the subject number. This number will be used throughout the trial.

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

The vaccination will be prepared and administered by the pharmacist or designee according to the instructions in the Pharmacy Manual or per manufacturer's instructions.

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

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

8.2.1 Precautions to be Observed in Administering the Investigational Vaccine

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

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

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

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

8.3 Randomization Code Creation and Storage

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

Randomization will be stratified by baseline dengue IgG status (positive / negative) measured by dengue IgG indirect ELISA performed on blood sample collected at screening. Inclusion in the CMI subset (approximately 80 subjects) will be on a voluntary basis.

8.4 Investigational Vaccine Blind Maintenance

This is a double-blind trial. The subjects, data collectors (e.g., Investigator), designated pharmacists/vaccine administrators and data evaluators (e.g., trial statisticians) are blinded.

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.

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

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

8.6 Accountability and Destruction of Sponsor-Supplied Vaccines

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.

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

Upon receipt of Sponsor-supplied vaccines, the Investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, the

investigational vaccine is received within the labeled storage conditions, and is in good condition. If quantity and conditions are acceptable, the Investigator or designee will acknowledge receipt of the shipment by recording in IWRS.

If there are any discrepancies between the packing list versus 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:

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

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

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

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

The pharmacist (or designated individual) at each site will be responsible for vaccine accountability and will document receipt, use, return, or destruction of HD-TDV and TDV. Vaccine accountability documentation will be reviewed by the 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

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

Informed consent must be obtained prior to the subject's entering into the trial, and before any protocol-directed procedures are performed. Note that this may be up to 28 days prior to Day 1 (Month 0).

After informed consent is obtained and if all eligibility criteria are fulfilled, the IWRS will assign a unique identification number to each subject. This will become the definitive subject number to be used throughout the trial. Subject numbers assigned to subjects who fail eligibility check (after being assigned a subject number through IWRS) should not be reused (Section 9.1.13), and similarly subject numbers assigned to subjects who withdraw or are discontinued between enrollment and Day 1 (Month 0) should not be reused.

9.1.2 Demographics, Medical History and Prior Medications

Demographic information to be obtained will include date of birth, gender, and race as described by the subject.

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

All medications (pharmaceutical products only) and vaccines taken or received by the subjects within 4 weeks prior to Day 1 (Month 0), blood products within 3 months prior to Day 1 (Month 0), and immunosuppressive therapy within 6 months prior to Day 1 (Month 0) are to be recorded on the Prior and Concomitant Medications eCRF. The use of antipyretics and/or analgesic medications within 24 hours prior to vaccination must be identified and the reason for their use (prophylaxis versus treatment) must be described in the source documents or the eCRF. Trial vaccination should be delayed if subjects have used antipyretics and/or analgesic medication within 24 hours prior to vaccine administration.

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

All concomitant therapy taken or received during the period starting with the administration of trial vaccine (Day 1 [Month 0]) and ending one month (minimum of 28 days) after vaccination must be recorded in the subject's source document and eCRF. Additionally, the receipt of any dose of any licensed dengue vaccine should be recorded throughout the trial using the concomitant medication page of the eCRF.

Prohibited Therapies are in Section 7.2.

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

9.1.3 Documentation of Trial Entrance/Randomization

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

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

9.1.4 Physical Examination

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

Targeted physical examination including but not limited to measurement of vital signs (See Section 9.1.5) will be performed at Day 1 (Month 0) and Day 365 (Month 12).

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

9.1.5 Vital Signs

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

Temperature measurement will be described in the Procedures Manual.

9.1.6 Screening

A blood sample (2.5 mL) will be collected at screening (28 days to 1 day prior to vaccination on Day 1 [Month 0]) for dengue IgG status assessment by dengue IgG indirect ELISA. All blood

samples will be collected in accordance with acceptable laboratory procedures. Blood samples will be processed in accordance with the Laboratory Guidelines as provided in the Procedures Manual.

9.1.7 Immunogenicity and CMI Assessments

Blood samples for immunogenicity evaluations will be collected at pre-vaccination on Day 1 (Month 0) and post-vaccination on Days 7, 15, 30 (Month 1), 60 (Month 2), 90 (Month 3), 180 (Month 6) and 365 (Month 12).

From approximately 80 subjects (approximately 40 subjects in each of the IgG positive and negative groups) who give consent to be included in the CMI subset, blood samples for characterization of CMI responses will be collected before vaccination on Day 1 (Month 0) and post-vaccination on Days 30 (Month 1), 60 (Month 2), 90 (Month 3), 180 (Month 6) and 365 (Month 12).

9.1.8 Viral Replication

Blood samples for assessment of vaccine viremia and CCI will be collected pre-vaccination on Day 1 (Month 0) and post-vaccination on Days 5, 7, 9, 11, 15, 17, 21 and 30 (Month 1).

All samples will be collected in accordance with acceptable laboratory procedures. The maximum volume of blood taken at any single visit is approximately 22.5 mL for subjects not included in the CMI subset and 62.5 mL for subjects included in the CMI subset. The approximate total volume of blood for the trial is maximum 137.5 mL for subjects not included in the CMI subset and 377.5 mL for subjects included in the CMI subset. Blood samples will be processed and stored at the trial site in accordance with the Laboratory Guidelines as provided in the Procedures Manual.

9.1.9 Processing, Labelling and Storage of Peripheral Blood Mononuclear Cells Samples

Peripheral Blood Mononuclear Cells (PBMCs) will be collected, processed, labeled and stored according to site standard operating procedures (SOP). Refer to the SOP for detailed instructions.

9.1.10 Safety Assessments

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

9.1.11 Contraception and Pregnancy Avoidance Procedure

For female subjects of childbearing potential, urine pregnancy testing will be performed at screening and prior to vaccination on Day 1 (Month 0). Subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy, donation of ova. Refer also to Section 7.2.

9.1.12 Pregnancy

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

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

If pregnancy occurs after administration of a blinded investigational vaccine, the Investigator must inform the subject 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.

9.1.13 Documentation of Subjects who are not Randomized

Investigators must account for all subjects who sign an informed consent. If a previously enrolled subject is found to be not eligible at Day 1 (Month 0), the Investigator should complete the eCRF. The IWRS should be contacted as a notification of non-randomization.

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

- Screen failure (did not meet inclusion criteria or did meet exclusion criteria).
- Withdrawal by subject.
- Site terminated by Sponsor.
- Study terminated by Sponsor.
- Other (Note: The specific reasons should be recorded in the "specify" field of the eCRF).

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

9.2 Monitoring Subject Treatment Compliance

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

9.3 Schedule of Observations and Procedures

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

9.3.1 Procedures During Screening (Day -28 to -1)

- Before performing any other trial procedure, the signed informed consent of the subject needs to be obtained. See Section 9.1.1.
- Check inclusion and exclusion criteria Refer to Sections 7.1 and 7.2.
- Collect demographic data, medical history, and concomitant medication. Refer to Section 9.1.2.
- Perform a complete physical examination. Refer to Section 9.1.4.
- Measure vital signs. Refer to Section 9.1.5.
- Perform urine pregnancy testing for female subjects of childbearing potential. Refer to Section 9.1.12.
- Collect blood sample. Refer to Section 9.1.7.

  Blood should be taken from the subject using aseptic venipuncture technique. Refer to the detailed collection and handling procedures outlined in the Procedures Manuals.
- The subject will receive a written reminder of the next planned trial activity.

9.3.2 Vaccination Procedures (Day 1 [Month 0])

- Prior to vaccination:
  - Check inclusion and exclusion criteria Refer to Sections 7.1 and 7.2.
  - Collect data on concomitant medication. Refer to Section 9.1.2.
  - Perform a targeted physical examination. Refer to Section 9.1.4.
  - Perform urine pregnancy testing for female subjects of childbearing potential. Refer to Section 9.1.12.
  - Check availability of the result of the dengue IgG indirect ELISA performed on blood sample collected at screening. Refer to Section 9.1.7.
- If subject meets all eligibility criteria:
  - Randomize subject. Refer to Section 9.1.3.
  - Collect blood sample. Refer to Sections 9.1.7, 9.1.8 and 9.1.9.

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 subject according to the assigned investigational vaccine. Refer to Section 8.1.3.
  - Perform injection site evaluation. Refer to Section 10.1.2.
- Distribute diary cards and perform following procedures (see also Section 10.4.2):

  - Careful training of the subject on how to measure the local injection site reactions, AEs and temperature, how to complete and how often to complete the diary card should be performed while the subject is under observation after vaccination.

- Diary card instruction must include the following:
  - The subject must understand that timely completion of the diary card on a daily basis is a critical component to trial participation. The subject should also be instructed to write clearly and to complete the diary card in pen. Any corrections to the diary card must only be performed by the subject by a single strikethrough line with a brief explanation for any change and be initialed and dated.
  - Starting on the day of vaccination, the subject will check for specific types of reactions at the injection site (solicited local AEs), any specific generalized symptoms (solicited systemic AEs), body temperature, unsolicited AEs, any other symptoms or change in the subject's health status, and any medications taken (excluding vitamins and minerals). These AEs (solicited and unsolicited) and body temperature will be recorded in the diary. Assessments should preferably take place in the evening at day's end.
  - Temperature measurement is to be performed using the thermometer provided by the trial site. If the subject feels unusually hot or cold during the day, the subject should check his/her temperature regularly. 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 (pain, erythema and swelling) is to be performed using the ruler provided by the site.
  - The collection on the diary card of solicited local AEs will continue for a total of 7 days following vaccine administration; this time period for solicited systemic AEs and body temperature will continue for a total of 14 days following vaccine administration. Unsolicited AEs will be collected on the diary card for 28 days following vaccination.
  - Subjects will be instructed to bring the diary card for solicited local AEs to the medical clinic on the Day 7 visit; the diary cards for solicited systemic AEs and unsolicited AEs will need to be returned on the Day 15 and Day 30 (Month 1) visits, respectively.
- After vaccination, the subject will be observed for at least 30 minutes including observation for unsolicited AEs, solicited AEs, and temperature measurement. Please take the opportunity to remind the subject how to measure solicited AEs and temperature as part of this observation period. Record all safety data collected in the subject's source documents.

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

9.3.3 Procedures at Post-Vaccination Visits (Days 5, 7, 9, 11, 15, 17, 21, 30 [Month 1], 60 [Month 2], 90 [Month 3] and 180 [Month 6])

- Perform symptom-directed physical examination. Refer to Section 9.1.4.
- Perform injection site evaluation on Day 7. Refer to Section 10.1.2.
- Measure vital signs on Days 9, 17 and 30 (Month 1). Refer to Section 9.1.5.
- Collect blood sample. Refer to Sections 9.1.7, 9.1.8 and 9.1.9.

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

- Review diary card with the subject on Days 7, 15 and 30 (Month 1):
  - The healthcare professional reviewing these data will discuss the AEs (if any) reported by the subject and will determine if any additional diagnoses and/or AEs are present and/or concomitant medications have been used.
  - Any newly described solicited and unsolicited safety information should be added to the diary card by the subject and initialed and dated.
  - Any illegible or implausible data should be reviewed with the subject. Any data that is identified as implausible or incorrect, and confirmed by the **subject** to be a transcription error should be corrected by the subject on the diary card (the correction should include a single strikethrough line and should be initialed and dated by the **subject)**. No corrections or additions to the diary card will be allowed after it is reviewed with the Investigator/ designee.

Please note:

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

1. No corrections or additions to the diary card will be allowed after it is delivered to the site.
2. Any blank or illegible fields on the diary card will be missing in the eCRF.
3. The site must enter all readable entries in the diary card onto the eCRF.

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

9.3.4 Final Visit (Day 365 [Month 12])

The final visit will be performed on Day 365 (Month 12). If a subject terminates earlier, standard visit procedures should be performed if possible. For all subjects receiving an investigational vaccine, the Investigator must complete the End of Trial eCRF page.

- Collect data on concomitant medication. The receipt of any dose of any licensed dengue vaccine should be recorded using the concomitant medication page of the eCRF. Refer to Section 9.1.2.
- Perform a targeted physical examination. Refer to Section 9.1.4.
- Collect blood sample. Refer to Sections 9.1.7 and 9.1.9.

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

9.3.5 Post-Trial Care

No post-trial care will be provided.

9.4 Biological Sample Retention and Destruction

In this trial, specimens for immune response testing will be collected as described in Section 9.1.7. After blood draw and serum processing, the serum samples will be preserved and retained at a central laboratory that was contracted by the Sponsor for this purpose for up to but not longer than 20 years or as required by applicable law. The Sponsor has put into place a system to protect the subjects' personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 AEs

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

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

The occurrence of unsolicited AEs will be measured for 28 days following vaccination and will be recorded on the "unsolicited AE" eCRF. These will be summarized in the final report under the category "unsolicited AEs" to differentiate them from other AEs which were solicited.

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

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

10.1.2 Solicited AEs

The occurrence of selected indicators of safety (Table 10.a) will be measured until Day 7 (solicited local reactions) and Day 14 (solicited systemic reactions) 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 AEs" to differentiate them from other AEs which were not solicited.

Table 10.a Local and Systemic AEs

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

(a) Fever is defined as greater than or equal to 38°C (100.4°F) regardless of method used [12].

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

Table 10.b Intensity of solicited safety parameters

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

(a) Fever is defined as greater than or equal to 38°C (100.4°F) regardless of method taken [12].

10.1.3 Serious Adverse Events (SAEs)

An SAE is defined as any untoward medical occurrence that:

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

10.2 Causality of AEs

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

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

10.2.1 Relationship to Trial Procedures

Relationship (causality) to trial procedures should be determined for all AEs. The relationship should be assessed as "Yes" if the Investigator considers that there is reasonable possibility that an event is due to a trial procedure. Otherwise, the relationship should be assessed as "No".

10.2.2 Outcome of AEs

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

10.3 Additional Points to Consider for AEs

An untoward occurrence generally may:

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

Diagnoses *vs.* signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, 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 are not considered AEs. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

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

10.4 Procedures

10.4.1 Collection and Reporting of AEs

All AEs, whether considered related with the use of the investigational vaccine or not, must be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report should be supplied, if possible. All findings must be reported on an AE eCRF and on the SAE form, if necessary (see Section 10.4.2). All findings in subjects experiencing AEs must also be reported in the subject's source documents. Any unsolicited AEs will be collected for 28 days on diary cards.

The following information will be documented for each event:

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

10.4.2 Collection and Reporting of Solicited AEs

The occurrence of selected indicators of safety will be collected on diary cards by the subjects until Day 7 (solicited local reactions) or Day 14 (solicited systemic reactions) and will be recorded on the "Local and Systemic Reactions" eCRF, as appropriate. Any solicited local or systemic AE observed as continuing on trial Day 7 (local reactions) or Day 14 (systemic reactions) will be recorded as an unsolicited AE on the AE eCRF. Any solicited local or systemic AE that resolved before that time but which recurs at a later time will be recorded as an unsolicited AE on the AE eCRF.

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

- Solicited local or systemic AEs that lead the subject to withdraw from the trial.
- Solicited local or systemic AEs that lead to the subject being withdrawn from the trial by the Investigator.
- Solicited local and systemic AEs that otherwise meet the definition of an SAE (see Section 10.1.2).

10.4.3 Collection and Reporting of SAEs

Collection of SAEs will commence from the time that the subject is administered the investigational vaccine (Day 1 [Month 0]). Routine collection of SAEs will continue until the end of the trial (Day 365 [Month 12]).

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 vaccines – if no unblinding is necessary, in a blinded way.
- Causality assessment.

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

10.5 Follow-up Procedures

10.5.1 AEs

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

10.5.2 SAEs

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

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

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

The Sponsor or designee will be responsible for the reporting of all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, Investigators and IRBs or IECs, as applicable, in accordance with national regulations 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.

10.5.4 Post-Trial Events

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

11.0 TRIAL-SPECIFIC REQUIREMENTS

No trial-specific committee will be used in this trial.

11.1 Trial-Specific Committees

11.1.1 Data Monitoring Committee

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

12.0 DATA HANDLING AND RECORDKEEPING

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

12.1 Electronic CRFs (eCRF)

Completed eCRFs are required for each subject who signs an informed consent.

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

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

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

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

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

12.2 Record Retention

The Investigator agrees to keep the records stipulated in Section 12.0 and those documents that include (but are not limited to) the trial-specific documents, the identification log of all participating subjects, medical records. Temporary media such as thermal sensitive paper should be copied and certified, source worksheets, all original signed and dated informed consent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent 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 vaccine indication being investigated or, if an application is not approved, until at least 2 years after the investigation is discontinued and regulatory authorities are notified. In addition, ICH E6 Section 4.9.5 states that the trial records should be retained until an amount of time specified by applicable regulatory requirements or for a time specified in the Clinical Study Site Agreement between the Investigator and Sponsor.

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

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A statistical analysis plan (SAP) will be prepared and finalized prior to the unblinding of the subjects' treatment assignment. 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 subjects' vaccination assignment. This review will assess the accuracy and completeness of the trial database, subject evaluability, and appropriateness of the planned statistical methods.

All analyses will be descriptive; no statistical hypotheses will be tested in this trial.

Note: Baseline dengue seropositivity (MNT) is defined as a reciprocal neutralizing titer ≥10 for one or more dengue serotype at baseline.

13.1.1 Analysis Sets

Safety Set: The Safety Set will consist of all randomized subjects who received the trial vaccine.

Full Analysis Set (FAS): The FAS will consist of all randomized subjects who received the trial vaccination and for whom a valid a pre-dose and at least one valid post-dose blood sample is taken.

Per-Protocol Set (PPS): The PPS will consist of subjects in the FAS who have no major protocol violations. The major protocol violation criteria will be defined as part of the blinded data review prior to the unblinding of subject's 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.

The primary analysis of immunogenicity and vaccine viremia endpoints will be based on the PPS; other supportive analysis may be provided for the FAS. The safety analysis will be based on the Safety Set.

13.1.2 Demographics and Other Baseline Characteristics

Age, gender, race, and other baseline characteristics will be summarized descriptively by treatment arm and baseline dengue seropositivity (MNT) for all randomized subjects.

13.1.3 Immunogenicity Analysis

For primary and secondary immunogenicity endpoints (i.e., GMTs of neutralizing antibodies and seropositivity rates [%] for each of the four dengue serotypes, descriptive statistics and 95% confidence intervals (CIs) will be provided by treatment arm (overall), and by treatment arm and baseline dengue seropositivity (MNT) for each applicable visit. Seropositivity is defined as a reciprocal neutralizing titer ≥10.

CMI data will be summarized descriptively.

13.1.4 Vaccine Viremia Analysis

For vaccine viremia endpoints (i.e., incidence, duration and level of vaccine viremia for each of the four dengue serotypes after vaccination), descriptive statistics and 95% CIs will be provided by treatment arm (overall), and by treatment arm and baseline dengue seropositivity (MNT) for each applicable visit.

13.1.5 Safety Analysis

All summaries of safety data will be performed using the Safety Set. The safety data will be summarized by treatment arm. For some key tables, the safety data will also be summarized by treatment arm and baseline dengue seropositivity (MNT). Full details will be provided in the SAP.

Solicited AEs

Solicited local AEs and solicited systemic AEs will be assessed by the use of diary cards for 7 days and 14 days, respectively, following vaccination (vaccination day included).

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 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 subjects with more than 1 episode of the same event, the maximum severity will be used for tabulations.

Unsolicited AEs

Unsolicited AEs will be assessed by the use of diary cards for 28 days following vaccination (vaccination day included).

Unsolicited AEs and SAEs will be coded according to MedDRA and summarized by SOC and PT. Adverse events leading to withdrawal will also be summarized.

All unsolicited AEs up to 28 days after 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 post-vaccination, 2) with onset between 1 and 14 days post-vaccination, and 3) with onset between 15 and 28 days post-vaccination.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis will be performed.

13.3 Determination of Sample Size

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

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Trial-Site Monitoring Visits

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

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

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 Food and Drug Administration [FDA], the United Kingdom Medicines and Healthcare Products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the trial site is contacted for an inspection by a regulatory body, the Sponsor should be notified immediately. The Investigator and institution guarantee access for quality assurance auditors to all trial documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE TRIAL

This trial will be conducted with the highest respect for the individual participants (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 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 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 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 form) reviewed; and state the approval date. The Sponsor will notify the site once the Sponsor has confirmed the adequacy of site regulatory documentation and, when applicable, the Sponsor has received permission from the competent authority to begin the trial. Until the site receives [notification] no protocol activities, including screening may occur.

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

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

15.2 Subject Information, Informed Consent, and Subject Authorization

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

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

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the Investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, 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 form and subject authorization form (if applicable) 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 form and subject authorization (if applicable) at the time of consent and prior to subject entering into the trial; however, the Sponsor may allow a designee of the Investigator to sign to the extent permitted by applicable law.

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

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record and eCRF, and the subject should receive a copy of the revised informed consent 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 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 center for this trial will provide the analyses needed for publication. Information regarding this trial will be posted on ClinicalTrials.gov.

15.4.2 Clinical Trial Registration

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

15.4.3 Clinical Trial Results Disclosure

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

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

15.5 Insurance and Compensation for Injury

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

16.0 REFERENCES

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

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

1. A statement that the trial involves research.
2. An explanation of the purposes of the research.
3. The expected duration of the subject's participation.
4. A description of the procedures to be followed, including invasive procedures.
5. The identification of any procedures that are experimental.
6. The estimated number of subjects involved in the trial.
7. A description of the subject's responsibilities.
8. A description of the conduct of the trial.
9. A statement describing the vaccination(s) and the probability for random assignment to each treatment.
10. A description of the possible side effects following vaccine administration that the subject may receive.
11. A description of any reasonably foreseeable risks or discomforts to the subject and, when applicable, to an embryo, fetus, or nursing infant.
12. A description of any benefits to the subject or to others that reasonably may be expected from the research. When there is no intended clinical benefit to the subject, the subject should be made aware of this.
13. Disclosures of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the subject and their important potential risks and benefits.
14. A statement describing the extent to which confidentiality of records identifying the subject will be maintained, and a note of the possibility that regulatory agencies, auditor(s), IRB/IEC, and the monitor may inspect the records. By signing a written informed consent form, the subject or the subject's 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 (either contained within the informed consent form or provided as a separate document) describing to the subject the contemplated and permissible uses and disclosures of the subject's personal information (including personal health information) for purposes of conducting the trial. The subject authorization must contain the following statements regarding the uses and disclosures of the subject's personal information:
    a) that personal information (including personal health information) may be processed by or transferred to other parties in other countries for clinical research and safety reporting purposes, including, without limitation, to the following: (1) Takeda, its affiliates, and licensing partners; (2) business partners assisting Takeda, its affiliates, and licensing partners; (3) regulatory agencies and other health authorities; and (4) IRBs/IECs;
    b) it is possible that personal information (including personal health information) may be processed and transferred to countries that do not have data protection laws that offer subjects the same level of protection as the data protection laws within this country; however, Takeda will make every effort to keep your personal information confidential, and your name will not be disclosed outside the clinic unless required by law;
    c) that personal information (including personal health information) may be added to Takeda's research databases for purposes of developing a better understanding of the safety and effectiveness of the investigational vaccine(s), studying other therapies for patients, developing a better understanding of disease, and improving the efficiency of future clinical 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., non-sterilized, premenopausal female subjects) who are sexually active must use adequate contraception (as defined in the informed consent) from signing of informed consent up to 6 weeks post-vaccination.

26. A statement that clinical trial information from this trial will be publicly disclosed in a publicly accessible website, such as ClinicalTrials.gov.

Signature Page for DEN-205 Protocol Amendment 2, Version 3.0, 25 April 2017
Title: A Phase II, Double-Blind, Randomized, Controlled Trial to Assess the Safe

Approval	PPD	
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