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

NCT Number: NCT02747927

Protocol Approve Date: 20 April 2021

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

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

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

PROTOCOL

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

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

Sponsor:	Takeda Vaccines, Inc. 40 Landsdowne Street Cambridge MA 02139 USA		
Trial Identifier:	DEN-301		
IND Number:	014292	**EudraCT Number:**	2018-003979-34
Vaccine Name:	Takeda's Tetravalent Dengue Vaccine Candidate (TDV)		
Date:	20 April 2021		
Amendment:	5		
Version:	Version 7.0 (supersedes Version 6.0)		

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

Table 1.a Contact Information

Issue	Contact
Serious adverse event and pregnancy reporting	PPD Fax and telephone numbers for serious adverse event and pregnancy reporting will be provided to the site.
Medical Monitor (medical advice on conduct of protocol or compound)	Emergency medical contact information will be provided to the site.
Responsible Medical Officer (carries overall responsibility for the conduct of the trial)	Emergency medical contact information will be provided to the site.

1.2 Approval

REPRESENTATIVES OF TAKEDA

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

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

SIGNATURES

PPD

INVESTIGATOR AGREEMENT

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

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

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

_____ _____
Signature of Investigator Date

_____
Investigator Name (print or type)

_____
Investigator's Title

_____
Location of Facility (City, State)

_____
Location of Facility (Country)

1.3 Protocol Amendment Summary of Changes

This document describes the changes in reference to the Protocol incorporating Amendment No. 5.

1.3.1 Amendment History

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

1.3.2 Summary of Changes

Amendment to Protocol Version 6.0 dated 18 May 2020

Rationale for the amendment:

This protocol amendment is to add a clarification that, due to the coronavirus disease 2019 (COVID-19) pandemic, alternative monitoring and data verification approaches may be used. In the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic, alternative monitoring approaches such as remote source data verification (SDV) or telephone contact may be used to ensure data quality and integrity and maintain subject safety.

Other modifications:

- The following modifications were made for alignment with protocol template Version 4.0:
  - Update in responsibilities of the signatory investigator(s).
  - Addition of trial risk management.
- Addition of remote source data verification (SDV).
- Addition of the EudraCT Number and reference to the EudraCT database.
- Addition of license and data of a first dengue vaccine.
- Update in the status of the Interim Clinical Study Reports planned for the trial.
- Administrative change of the details of Takeda representatives.
- Updated list of Abbreviations.
- Correction and update of list of References.

Details of the changes that have been made in this amendment are outlined below. New text is shown in bold italics and any deleted text is marked using strikethrough.

Section	Description of change	
Title page	***EudraCT Number:***	***2018-003979-34***
1.2	**REPRESENTATIVES OF TAKEDA** PPD	
1.3	This document describes the changes in reference to the Protocol incorporating Amendment No. ~~3~~ ***5***	
2.0	EudraCT No.: ~~not applicable~~ ***2018-003979-34*** ~~No licensed dengue vaccine is available at the time of the writing of this protocol nor is there an antiviral therapy for dengue virus infection.~~ Treatment of dengue fever is based solely on symptoms and signs, with fluid replacement required for hemorrhagic or shock cases. ***No antiviral therapy for dengue virus infection is available***. Preventive measures ***that*** rely on mosquito control and individual protection, are of limited efficacy, complex to implement and questionable in terms of cost-effectiveness. There is a great unmet global public health need for a safe and effective vaccine that will protect against all serotypes of dengue infection, and thereby reduce the morbidity and mortality associated with dengue disease. ***A first recombinant dengue vaccine (chimeric yellow fever virus-dengue virus tetravalent dengue vaccine [CYD-TDV]) has been approved since 2015 in several Asian and Latin American countries as well as in the United States and in the European Union. Clinical data indicate an unfavorable risk-benefit profile for children aged <9 years with this first approved vaccine. Additionally, vaccine efficacy was different between serotypes and depended on dengue pre-exposure status. More recent analyses found that people who had not been infected by dengue virus before vaccination had a higher risk of getting severe disease when they were infected with dengue virus after vaccination with CYD-TDV. In a revised Strategic Advisory Group of Experts on Immunization (SAGE) recommendation in April 2018, the SAGE concluded that for countries considering CYD-TDV vaccination as part of their dengue control program, a "pre-vaccination screening strategy" would be the preferred option, in which only dengue-seropositive persons are vaccinated***. ***Hence, there is a continued unmet public health need for safer and more efficacious dengue vaccines.***	

Section	Description of change
2.0	**Investigational Vaccine:** **Parts 1, 2, and 3** • Control: Placebo ~~will be~~ was Normal Saline ***for injection (0.9% sodium chloride solution)*** ~~for injection~~.
2.0	At the time of this protocol amendment, an Interim Clinical Study Report ***(CSR)*** has been prepared for the results from the dry-run, Part 1, and Part 2 ***and a.*** ~~A~~ second Interim ~~Clinical Study Report~~ ***CSR has been*** ~~will be~~ prepared for data until 6 months after the end of Part 2 (2-year follow-up post-second dose). ***A third interim CSR will be prepared for data until 18 months after the end of Part 2 (3-year follow-up post-second dose)***. Additional reports for the results from Parts 3, CCI including further Interim ***CSRs*** ~~Clinical Study Reports~~, will be prepared if required for internal use and/or for regulatory submission. A Final ~~Clinical Study Report~~ ***CSR*** will be prepared upon trial completion and will include results for the trial duration.
2.0 6.2.1	Amended text covers Part 1, 2, and 3: In order to maintain the double-blind design, a placebo (Normal Saline) ~~will be~~ ***was*** used in this trial. A placebo has~~***d***~~ been chosen to avoid the use of a number of active vaccine comparators that would be required due to the wide age range of subjects (4 to 16 years of age) and the diverse countries participating. As no active comparator ~~is~~ ***was*** possible as part of the trial design, a licensed vaccine will be offered to all subjects, irrespective of their full participation in this trial and at least 6 months after any protocol defined vaccination. The choice of this vaccine ~~will be~~ ***was*** discussed between the Sponsor and the Investigator, and ~~will be~~ ***was*** approved by the appropriate ethics committee. This vaccine will be used according to the labeling approved in the country.
2.0, 4.2.2, 6.2.2	CCI [redacted]
2.1	**Table 2.d Schedule of Trial Procedures for Parts 1, 2 and 3** ***Note: when a site visit cannot be carried out due to the coronavirus disease 2019 (COVID-19) pandemic, alternative methods of contact (eg, telephone contact) will be made for subjects who are still under monitoring for safety reporting.*** CCI [redacted]

Section	Description of change	
3.0	***3.2 Principal Investigators/Coordinating Investigators*** ***Selection criteria for the principal investigators and coordinating investigators will include significant knowledge of the trial protocol, the investigational vaccine, their expertise in the therapeutic area and the conduct of clinical research as well as trial participation. Takeda will select one or more signatory/signatories from the investigators who participate in the study. The signatory coordinating investigator(s) will be required to review and sign the clinical protocol. The signatory coordinating investigator(s) will also be required to review and sign the Clinical Study Report(s) (CSR[s]) and by doing so agree(s) that it accurately describes the results of the trial.***	
3.3	***CSR(s)***	***Clinical Study Report(s)***
	CYD-TDV	***Chimeric yellow fever virus-dengue virus tetravalent dengue vaccine***
	EudraCT	***European Union Drug Regulating Authorities Clinical Trials***
	QTL	***Quality Tolerance Limits***
	SAGE	***Strategic Advisory Group of Experts on Immunization***
	SDV	***Source data verification***
4.1	~~No licensed dengue vaccine is available at the time of the writing of this protocol nor is there an antiviral therapy for dengue virus infection.~~ Treatment of dengue fever is based solely on symptoms and signs, with fluid replacement required for hemorrhagic or shock cases. ***No antiviral therapy for dengue virus infection is available***. Preventive measures ***that*** rely on mosquito control and individual protection, are of limited efficacy, complex to implement and questionable in terms of cost-effectiveness. There is a great unmet global public health need for a safe and effective vaccine that will protect against all serotypes of dengue infection, and thereby reduce the morbidity and mortality associated with dengue disease ~~[4-10]~~ ***[1-7]***. ***A first recombinant dengue vaccine (chimeric yellow fever virus-dengue virus tetravalent dengue vaccine [CYD-TDV]) has been approved since 2015 in several Asian and Latin American countries [8] as well as in the United States and in the European Union. Clinical data indicate an unfavorable risk-benefit profile for children aged <9 years with this first approved vaccine. Additionally, vaccine efficacy was different between serotypes and depended on dengue pre-exposure status [9]. More recent analyses found that people who had not been infected by dengue virus before vaccination had a higher risk of getting severe disease when they were infected with dengue virus after vaccination with CYD-TDV [10]. In a revised Strategic Advisory Group of Experts on Immunization (SAGE) recommendation in April 2018, the SAGE concluded that for countries considering CYD-TDV vaccination as part of their dengue control program, a "pre-vaccination screening strategy" would be the preferred option, in which only dengue-seropositive persons are vaccinated [11].*** ***Hence, there is a continued unmet public health need for safer and more efficacious dengue vaccines [12].*** The efficacy against hospitalized dengue for Year 2 was 76.1% (95% CI: 50.8 to 88.4%) versus 95.4% (95% CI: 88.4-98.2) for Year 1 [~~13~~***15, 16***].	

Section	Description of change
4.2.1	In order to maintain the double-blind design, a placebo (Normal Saline) ~~will be~~ ***was*** used in this trial. A placebo has~~***d***~~ been chosen to avoid the use of a number of active vaccine comparators that would be required due to the wide age range of subjects (4 to 16 years of age) and the diverse countries participating. As no active comparator ~~is~~ ***was*** possible as part of the trial design, a licensed vaccine will be offered to all subjects, irrespective of their full participation in this trial and at least 6 months after any protocol defined vaccination. The choice of this vaccine ~~will be~~ ***was*** discussed between the Sponsor and the Investigator, and ~~will be~~ ***was*** approved by the appropriate ethics committee. This vaccine will be used according to the labeling approved in the country (see also Section 9.3.3).
8.1.2.1	*8.1.2.1.1 Parts 1, 2, and 3* • **Placebo (Normal Saline) control** The placebo ~~will be~~ ***was*** normal saline ***for injection*** (0.9% ***sodium chloride*** solution) ~~for injection~~
9.3.1, 9.3.2	***When a site visit cannot be carried out due to the COVID-19 pandemic, alternative methods of contact (eg, telephone contact) will be made for subjects who are still under monitoring for safety reporting.***
9.3.3.1	The choice of this vaccine ~~will be~~ ***was*** discussed between the Sponsor and the Investigator, and ~~will be~~ ***was*** approved by the appropriate ethics committee.
12.1	***When a site visit cannot be carried out due to the COVID-19 pandemic, alternative methods of contact (eg, telephone contact) will be made for subjects who are still under monitoring for safety reporting. Refer also to Section 14.1.***
13.2.3	At the time of this protocol amendment, an Interim ~~Clinical Study Report~~ ***CSR*** has been prepared for the results from the dry-run, Part 1, and Part 2 ***and a***~~***.*** A~~ second Interim ~~*Clinical Study Report*~~ ***CSR has been*** ~~will be~~ prepared for data until 6 months after the end of Part 2 (2-year follow-up post-second dose). ***A third interim CSR will be prepared for data until 18 months after the end of Part 2 (3-year follow-up post-second dose)***. Additional reports for the results from Parts 3, CCI including further Interim ~~Clinical Study Reports~~ ***CSRs***, will be prepared if required for internal use and/or for regulatory submission. A Final ~~Clinical Study Report~~ ***CSR*** will be prepared upon trial completion and will include results for the trial duration.
14.1	***In the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic, alternative monitoring approaches such as remote source data verification (SDV) or telephone contact may be used to ensure data quality and integrity and maintain subject safety. Alternative monitoring approaches should be used only where allowed by the local Health Authority and when approved by the IRB/IEC. Site staff will inform each trial participant or designated legal representative and ensure that they do not object to the remote review of their records for trial purposes and document this process in the trial participant's medical records. If a trial participant objects to remote review of their records, no remote SDV will occur for that trial***

Section	Description of change
14.1	***participant. During remote monitoring, the monitor should focus on trial activities that are essential to the safety of trial subjects and/or data reliability.***
14.0	***14.4 Trial Risk Management*** ***The ICH E6 addendum (R2) guidance encourages a risk-based approach to the management of clinical trials and includes requirements for risk control and risk reporting. Takeda or designee (CRO) has established Quality Tolerance Limits (QTL), taking into consideration the medical and statistical characteristics of the variables and the statistical design of this trial. This process was performed according to Takeda internal procedures.*** ***At the end of the trial, the quality management approach implemented will be described in the CSR. If applicable, the CSR will summarize important deviations from the predefined QTL and the remedial actions taken.***
15.3	To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the Sponsor requires the Investigator to permit its monitor or designee's monitor, representatives from any regulatory authority (eg, US FDA, ***regulatory authorities of an European / European Economic Area Member State,*** Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the Sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, electrocardiogram (ECG) reports, admission and discharge summaries for hospital admissions occurring during a subject's trial participation, and autopsy reports. ***In the event a monitor cannot visit the site in a timely manner due to the COVID-19 pandemic, alternative monitoring approaches such as remote source data verification or telephone contact may be used to ensure data quality and integrity and maintain subject safety (refer also to Section 14.1).***
15.4.1	Information regarding this trial will be posted on ClinicalTrials.gov ***and the European Union Drug Regulating Authorities Clinical Trials (EudraCT) websites***.
15.4.2	In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable law, regulation and guidance, the Sponsor will, at a minimum register all clinical trials conducted in subjects that it sponsors anywhere in the world on ClinicalTrials.gov***, EudraCT*** or other publicly accessible websites before trial initiation.
15.4.3	The Sponsor will post the results of this clinical trial, regardless of outcome, on ClinicalTrials.gov***, EudraCT*** or other publicly accessible websites, as required by applicable laws and/or regulations.

Section	Description of change
16.0	~~2. Villar L, Dayan GH, Arredondo-García JL, Rivera DM, Cunha R, Deseda C, et al. Efficacy of a tetravalent dengue vaccine in children in Latin America. N Engl J Med 2015; 372(2):133-23.~~ ~~3. Capeding MR, Tran NH, Hadinegoro SR, Ismail HI, Chotpitayasunondh T, Chua MN, et al. Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomized, observer-masked, placebo-controlled trial. Lancet 2014; 384(9951):1358-65.~~ ~~7~~ ***4***. World Health Organization, Dengue and severe dengue. World Health Organization, Geneva, Switzerland, 2018. (Available at: http://www.who.int/mediacentre/factsheets/fs117/en/) (accessed ~~18 May 2020~~ ***20 April 2021***). ~~8~~ ***5***. World Health Organization. Dengue hemorrhagic fever: diagnosis, treatment, prevention and control, 2nd Edn. Geneva: World Health Organization. 1997. (Available at: http://www.who.int/csr/resources/publications/dengue/Denguepublication/en/) (accessed ~~18 May 2020~~ ***20 April 2021***). ***8. Wichmann O, Vannice K, Asturias EJ, de Albuquerque Luna EJ, Longini I, Lopez AL, et al. Live-attenuated tetravalent dengue vaccines: The needs and challenges of post-licensure evaluation of vaccine safety and effectiveness. Vaccine. 2017. 35(42):5535-42.*** ~~1.~~ ***9.*** Hadinegoro SR, Arredondo-García JL, Capeding MR, Deseda C, Chotpitayasunondh T, Dietze R, et al. Efficacy and long-term safety of a dengue vaccine in regions of endemic disease. N Engl J Med 2015; 373(13):1195-206 ***10. Sridhar S, Luedtke A, Langevin E, Zhu M, Bonaparte M, Machabert T, et al. Effect of dengue serostatus on dengue vaccine safety and efficacy. N Engl J Med. 2018. 379(4):327-40.*** ***11. Revised SAGE recommendation on use of dengue vaccine. April 2018. Available at https://www.who.int/immunization/diseases/dengue/revised_SAGE_recommendations_d ngue_vaccines_apr2018/en/ [Accessed 20 April 2021].*** ***12. World Health Organization. Weekly Epidemiological Record. 2018. 93:329-44. Available at http://www.who.int/wer [Accessed 20 April 2021].*** ~~13~~ ***15***. Biswal S, Borja-Tabora C, Martinez Vargas L, Velásquez H, ~~Theresea~~ Alera M***T***, Sierra V et al. Efficacy of a tetravalent dengue vaccine in healthy children aged 4-16 years: a randomized, placebo-controlled, phase 3 trial. ~~The~~ Lancet 2020***;*** ~~[Epub ahead of print]~~ ***395(10234):1423-33***. ***16. Lopez-Medina E, Biswal S, Saez-Llorens X, Borja-Tabora C, Bravo L, Sirivichayakul C, et al. Efficacy of a dengue vaccine candidate (TAK-003) in healthy children and adolescents two years after vaccination. J Infect Dis 2020 [Epub ahead of print]***. ~~14~~ ***17***. Tetravalent Dengue Vaccine Candidate (TDV) Global Investigator's Brochure Edition ~~10~~ ***11*** 26 June ~~2019~~ ***2020***
Appendix A	14 Review and provide a signature as approval of the content of the ~~Clinical Study Report~~ ***CSRs***.

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2.0 TRIAL SUMMARY

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

Background:

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

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

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

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

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

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

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

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

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

CCI

[redacted]

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

Rationale for the Proposed Phase III Efficacy Trial:

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

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

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

Parts 1, 2, and 3

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

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

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

CCI [redacted]

Trial Design:

This is a phase III, double-blind, randomized, placebo-controlled trial with 2 parallel groups. The trial includes for all subjects at least 3 time periods (Parts 1, 2 and 3) for surveillance of febrile illness with potential dengue etiology. CCI [redacted].

The trial design and subject population for Parts 1, 2, and 3 of the trial CCI [redacted] are below.

Parts 1, 2, and 3

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

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

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

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

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

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

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

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

Definition of active surveillance

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

Duration of active surveillance

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

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

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

Aspects of modified active surveillance (Part 3):

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

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

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

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

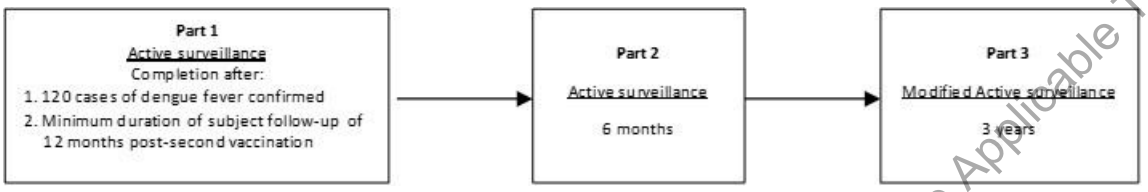


Table 2.a Differences between Active Surveillance (Dry-Run, Parts 1 and 2) and Modified Active Surveillance (Part 3)

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

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

Case definition for efficacy objectives:

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

Handling of febrile illness cases (suspected dengue cases):

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

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

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

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

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

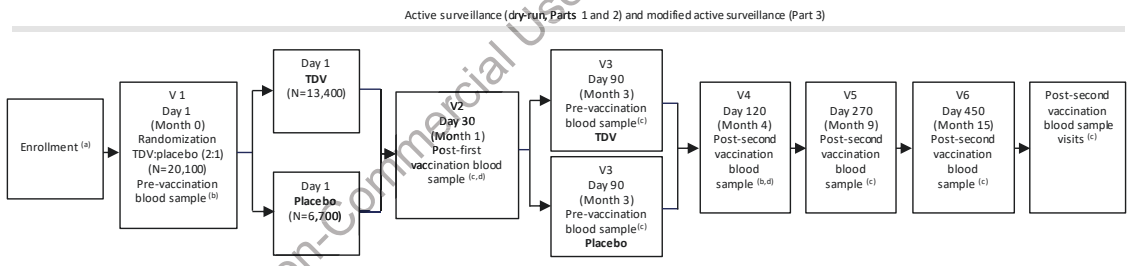
A febrile illness as described above will require an interval of at least 14 days from a previous febrile illness to avoid overlap of acute and convalescent visits from 1 episode with those from a second episode.

Procedures

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

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

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



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

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

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

All subjects:

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

Subset:

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

Safety evaluation:

All subjects:

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

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

Subset:

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

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Handling of febrile illness cases (suspected dengue cases):

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

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

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

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

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

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Primary Objective:

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

Secondary Objectives:

To be assessed post-second vaccination:

Efficacy:

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

Safety:

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

Immunogenicity:

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

Exploratory Objectives:

PPD

Subject Population:

Healthy subjects: Yes.

Parts 1, 2, and 3:

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

Planned Number of Subjects: 20,100.

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

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Criteria for Inclusion:

Trial entry

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

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[redacted]

Criteria for Exclusion:

Trial entry

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

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

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

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

[2] Hormonal contraceptive (such as oral, injection, transdermal patch, implant, cervical ring); barrier (condom with spermicide or diaphragm with spermicide) each and every time during intercourse; intrauterine device (IUD); monogamous relationship with vasectomized partner (partner must have been vasectomized for at least 6 months prior to Day 1 [Month 0]). Other contraceptive methods may be considered in agreement with the Sponsor and will be approved by the appropriate ethics committee.

iii. CCI [redacted]
iv. Receipt of immunostimulants within 60 days prior to Day 1b (Month 0b).
v. Immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy within 6 months prior to Day 1b (Month 0b).
vi. HIV infection or HIV-related disease.
vii. Genetic immunodeficiency.

3. Receipt of any other vaccine within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to Day 1b (Month 0b), or planning to receive any vaccine within 28 days after Day 1b (Month 0b).
4. CCI [redacted]
5. Participation in any clinical trial of a dengue candidate vaccine other than the current trial, or receipt of a dengue vaccine other than the trial vaccine at any time during participation in this trial.
6. First degree relatives of individuals involved in trial conduct.
7. Females of childbearing potential who are sexually active, and who have not used any of the acceptable contraceptive methods as specified under the criteria for entry into the trial, for at least 2 months prior to Day 1b (Month 0b) (see also trial entry inclusion criteria #5).
8. CCI [redacted]
9. Deprived of freedom by administrative or court order, or in an emergency setting, or hospitalized involuntarily at any time during participation in this trial.
10. CCI [redacted]
11. Identified as an employee of the Investigator or trial center, with direct involvement in the present trial or

CCI [redacted]

Criteria for delay of second trial vaccination:

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

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

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

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Investigational Vaccine:
Parts 1, 2, and 3

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

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

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Period of Evaluation:
For the duration of a subject's participation.

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

Secondary endpoints:

Efficacy

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

Safety

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

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

All subjects:

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

Immunogenicity

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

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

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

Exploratory endpoints:

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Statistical considerations:

Analysis sets – Parts 1, 2, and 3

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

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

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

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

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

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

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Efficacy analysis

Parts 1, 2, and 3

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

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

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

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

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

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

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

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

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

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

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

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

Vaccine immunogenicity analysis

Parts 1, 2, and 3

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

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Safety Analysis

Parts 1, 2, and 3

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

Reactogenicity

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

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

Unsolicited AEs

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

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

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

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Interim Analyses and reporting:

Interim analyses are planned for Part 1, Part 2, 2-year follow-up post-second dose, 3-year follow-up post-second dose, at the end of Part 3, 30 days (1 month) CCI [redacted]

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

Sample size justification:

Parts 1, 2, and 3

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

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

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

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Data Monitoring Committee:

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

2.1 Schedule of Trial Procedures

Table 2.d presents the schedule of trial procedures for Parts 1, 2, and 3. Table 2.e presents the schedule of trial procedures CCI [redacted]

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

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

Continued

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

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

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

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

(r) At 30 minutes after vaccine administration on the day of vaccinations.
(s) Diary cards will be distributed for the collection of solicited local adverse events (AEs) until Day 7 (day of vaccination + 6 subsequent days), and of solicited systemic AEs until Day 14 (day of vaccination + 13 subsequent days) after each vaccination.
(t) Unsolicited AEs will be collected up to 28 days after each vaccination by interview.
(u) Additional blood samples for dengue neutralizing antibodies will be collected for subjects in the subset post first vaccination on Day 30 (Month 1), pre-vaccination on Day 90 (Month 3), post-second vaccination on Day 270 (Month 9), Day 450 (Month 15), and then every 12 months until the end of Part 3.
(v) Between 4 years and approximately 4.5 years post-dose 2 in Part 3, the parent/guardian of subjects who are included in the subset from Parts 1, 2, and 3 (see footnote 'm') and the PPS, and were 4 to 11 years of age at the time of randomization in the trial (Day 1 [Month 0]) w[redacted]. Details on data analysis for subjects who do not complete Part 3 of the trial will be provided in the Statistical Analysis Plan.

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[redacted]

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