Title: A Phase 3, Open-Label, Randomized Trial to Investigate the Immunogenicity and Safety of the Co-administration of a Subcutaneous Dengue Tetravalent Vaccine (Live, Attenuated) (TDV) and an Intramuscular Recombinant 9-Valent Human Papillomavirus (9vHPV) Vaccine in Subjects Aged ≥9 to <15 Years in an Endemic Country for Dengue

NCT Number: NCT04313244

Protocol Approve Date: 03 March 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 or company confidential information.

PROTOCOL

A Phase 3, Open-Label, Randomized Trial to Investigate the Immunogenicity and Safety of the Co-administration of a Subcutaneous Dengue Tetravalent Vaccine (Live, Attenuated) (TDV) and an Intramuscular Recombinant 9-Valent Human Papillomavirus (9vHPV) Vaccine in Subjects Aged ≥9 to <15 Years in an Endemic Country for Dengue

Immunogenicity and Safety of TDV and 9vHPV in Subjects Aged ≥9 to <15 Years

Sponsor:	Takeda Vaccines, Inc. 40 Landsdowne Street Cambridge, MA, 02139 USA
Trial Identifier:	DEN-308
IND Number:	Not Applicable **EudraCT Number:** Not Applicable
Trial Vaccine Name:	*Investigational vaccine* Dengue Tetravalent Vaccine (Live Attenuated) (TDV) comprised of a molecularly characterized, attenuated dengue serotype 2 strain (TDV-2), a dengue serotypes 2/1 recombinant strain (TDV-1), a dengue serotypes 2/3 recombinant strain (TDV-3), and a dengue serotypes 2/4 recombinant strain (TDV-4). *Concomitant vaccine* Recombinant 9-Valent Human Papillomavirus (9vHPV) vaccine containing the L1 proteins for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58.
Takeda Approval Date:	03 March 2021
Version:	Version 5.0

1.0 ADMINISTRATIVE INFORMATION

1.1 Contacts

Issue	Contact
Serious adverse event and pregnancy reporting	[redacted]

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 [1].
- International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH), E6 (R2) Good clinical practice (GCP): Consensus guideline [2].
- All applicable laws and regulations, including, but not limited to those related to data privacy and clinical trial disclosure.

SIGNATURES

{See appended signature page}

[redacted]

Date

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Date

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[redacted]

Date

{See appended signature page}

[redacted]

Date

INVESTIGATOR AGREEMENT

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

- The ethical principles that have their origin in the Declaration of Helsinki [1].
- ICH E6 (R2), GCP: Consensus guideline [2].
- All applicable laws and regulations, including, but not limited to those related to data privacy and clinical trial disclosure.
- Regulatory requirements for reporting serious adverse events (SAEs) defined in Section 10.4.4 of this protocol.
- Terms outlined in the Clinical Trial Site Agreement.
- Appendix A – Responsibilities of the investigator.

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

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State)

Location of Facility (Country)

1.3 Protocol Version Summary of Changes

This document describes the changes in reference to the protocol incorporating Amendment No. 2 (Version 4).

1.3.1 Version History

Date	Version Number	Change Type	Region
09 July 2018	1.0 (internal)	Not applicable	Global
02 December 2019	2.0 (initial protocol)	Not applicable	Global
10 August 2020	3.0 (amendment 1)	Non-substantial	Global
03 March 2021	4.0 (internal)	Not applicable	Global
03 March 2021	5.0 (amendment 2)	Substantial	Global

1.3.2 Summary of Changes

Amendment to Protocol Version 3.0, 10 August 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.

- Addition of a clarification that some of the test results may not be available prior to database lock because some trial laboratory procedures are not carried out during the COVID-19 pandemic.

Other modifications:

- The following modifications were made for alignment with protocol template Version 4.0:
  - Update in responsibilities of the signatory investigator.
  - Addition of trial risk management.
- Administrative change of the details of the medical director and clinical project oversight manager.
- Deletion of proprietary table showing lower limits of quantification and serostatus cut-offs for each of the 9 vaccine HPV types.
- Few minor editorial changes.

Details of the changes are outlined below. In this section only (ie, not in the protocol body) all new text is shown in bold italics and any redundant text is marked using strikethrough.

Section	Description of change
Title page	Date: ~~10 August 2020~~ ***03 March 2021*** Version ~~3.0~~ ***5.0***
1.2	[redacted]
	[redacted]
2.0 and 5.2.2	Deletion of proprietary table containing lower limits of quantification and serostatus cut-offs for each of the 9 vaccine HPV types and cross referral to the statistical analysis plan added instead. ~~The lower limits of quantification and serostatus cut-offs for each of the 9 vaccine HPV types are shown below.~~ ***For the lower limits of quantification and serostatus cut-offs for each of the 9 vaccine HPV types, please refer to the statistical analysis plan (SAP).***
2.0	Handling of missing data will be described in ~~the statistical analysis plan (SAP)~~ ***SAP***.
2.1	Table 2.a Schedule of Trial Procedures (Visits 1 to 7 [Day 1 (M0) to Day 360 (M12)]) ***Note: When a site visit cannot be carried out due to the coronavirus disease 2019 (COVID-19) pandemic, alternative methods of contact (e.g telephone contact) will be made for subjects who are still under monitoring for safety reporting.***

Section	Description of change
3.2	~~The sponsor will select a signatory principal investigator (PI)/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 PI/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.~~ ***Selection criteria for the principal investigator (PI) 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 a signatory investigator from the investigators who participate in the study. The signatory investigator will be required to review and sign the clinical protocol. The signatory investigator will also be required to review and sign the clinical study report (CSR) and by doing so agrees that it accurately describes the results of the trial.***
3.3	***QTL Quality tolerance limits***
8.4	To prevent bias or the perception of bias, study team members responsible for decision making regarding study conduct or analysis of data after the first subject enrollment (eg protocol ~~deviation review, protocol~~ amendment and ~~statistical analysis plan [SAP]~~ ***SAP*** amendment) will be documented in the data access management plan, and will be independent of unblinded data review.
9.1.5	~~Body temperature measurement will be described in the Procedures Manual.~~
9.3.1	Blood should be taken from the subject using an aseptic venipuncture technique for serological immunogenicity testing. ~~Refer to the detailed collection and handling procedures outlined in the Procedures Manuals.~~
9.3.4	Blood should be taken from the subject using an aseptic venipuncture technique for serological immunogenicity testing. ~~Refer to the detailed collection and handling procedures outlined in the Procedures Manuals.~~
9.3.6	~~Not applicable.~~ ***When a site visit cannot be carried out due to the COVID-19 pandemic, alternative methods of contact (e.g telephone contact) will be made for subjects who are still under monitoring for safety reporting.***
12.1	***When a site visit cannot be carried out due to the COVID-19 pandemic, alternative methods of contact (e.g telephone contact) will be made for subjects who are still under monitoring for safety reporting. Refer also to Section 14.1.***

Section	Description of change
14.0	**14.1 Trial-Site Monitoring Visits** ***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. Alternative monitoring approaches should be used only where allowed by the local Health Authority and when approved by the IRB/IEC. During remote monitoring, the monitor should focus on trial activities that are essential to the safety of trial subjects and/or data reliability.*** ***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 established quality tolerance limits (QTL) taking into consideration the medical and statistical characteristics of the variables and the statistical design of the 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.***

Section	Description of change
16.0	2. International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH harmonised guideline. Integrated Addendum to ICH E6 (R1): Guideline for Good Clinical Practice ICH E6 (R2): ICH Consensus Guideline. Available at https://www.fda.gov/media/93884/download [Accessed ~~10 August 2020~~ ***03 March 2021].***
	7. World Health Organization, 2019. Dengue and severe dengue. Fact Sheet. Available at https://www.who.int/en/news-room/fact-sheets/detail/dengue-and-severe-dengue [Accessed ~~10 August 2020~~ ***03 March 2021].***
	8. World Health Organization, 1997. Dengue hemorrhagic fever: diagnosis, treatment, prevention and control, 2nd Edition. Geneva. Available at http://www.who.int/csr/resources/publications/dengue/Denguepublication/en/ [Accessed ~~10 August 2020~~ ***03 March 2021].***
	9. World Health Organization, 2009. Dengue guidelines for diagnosis, treatment, prevention and control. Available at http://www.who.int/tdr/publications/documents/dengue-diagnosis.pdf. [Accessed ~~10 August 2020~~ ***03 March 2021].***
	14. Revised SAGE recommendation on use of dengue vaccine. April 2018. Available at https://www.who.int/immunization/diseases/dengue/revised_SAGE_recommendations_dengue_vaccines_apr2018/en/ [Accessed ~~10 August 2020~~ ***03 March 2021].***
	15. World Health Organization. Weekly Epidemiological Record. 2018. 93:329-44. Available at http://www.who.int/wer [Accessed ~~10 August 2020~~ ***03 March 2021].***
	18. World Health Organization. Human papillomavirus (HPV). Available at http://www.who.int/immunization/diseases/hpv/en/ [Accessed ~~10 August 2020~~ ***03 March 2021].***
	19. Merck. Gardasil 9 prescribing information. Available at https://www.fda.gov/media/90064/download [Accessed ~~10 August 2020~~ ***03 March 2021].***
	22. Policy and communication bulletin – The clinical center. Guidelines for limits of blood drawn for research purposes in the clinical center. Manual transmittal sheet, no. M95-9 (rev.), 2009. Available at https://irb.research.chop.edu/sites/default/files/documents/g_nih_blooddraws.pdf [Accessed ~~10 August 2020~~ ***03 March 2021].***

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

2.0 TRIAL SUMMARY

Name of Sponsor: Takeda Vaccines, Inc. 40 Landsdowne Street, Cambridge, MA 02139, USA		**Product Name:** Dengue Tetravalent Vaccine (Live, Attenuated) (TDV)
Trial Title: A Phase 3, Open-Label, Randomized Trial to Investigate the Immunogenicity and Safety of the Co-administration of a Subcutaneous Dengue Tetravalent Vaccine (Live Attenuated) (TDV) and an Intramuscular Recombinant 9-Valent Human Papillomavirus (9vHPV) Vaccine in Subjects Aged ≥9 to <15 Years in an Endemic Country for Dengue		
IND No.: Not applicable		**EudraCT No.:** Not applicable
Trial Identifier: DEN-308	**Phase:** 3	**Blinding Schema:** Open-label
Indication: Prevention of dengue fever of any severity due to any serotype		

Background:

Dengue fever is caused by infection with the wild type dengue virus (DENV), a ribonucleic acid virus that occurs as 4 recognized serotypes, DENV-1, DENV-2, DENV-3, or DENV-4. These dengue viruses are transmitted to humans by mosquitoes (primarily *Aedes aegypti*). The 4 dengue viruses are endemic in Asia, Central and South America, the Caribbean, the Pacific Islands, and parts of Africa. There are an estimated 390 million dengue infections per year worldwide, which is more than 3 times the previous World Health Organization (WHO) estimate of 50 to 100 million cases. Every year, around 500,000 cases of dengue hemorrhagic fever (DHF) require hospitalization with an estimated death rate of 2.5%, primarily in children. It is estimated that 3.9 billion people are at risk of dengue infection.

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

Treatment of dengue fever is based solely on medical management of signs and symptoms, with fluid replacement required for hemorrhagic or shock cases. An antiviral therapy for dengue virus infection is not available at this time. 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 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.

Dengue Tetravalent Vaccine (Live, Attenuated) (TDV) – Background:

The investigational vaccine TDV, also known as TAK-003, consists of 1 molecularly characterized, attenuated dengue

virus serotype 2 strain denoted as the dengue virus serotype 2 backbone and 3 recombinant dengue virus strains expressing surface antigens corresponding to DENV serotypes 1-4. The dengue virus serotype 2 backbone is based upon the attenuated laboratory-derived DENV-2 virus strain, originally isolated at Mahidol University, Bangkok, Thailand and generated by 53 serial passages in primary dog kidney (PDK) cells (DENV-2 PDK-53). The recombinant, attenuated vaccine strains for dengue serotypes 1, 3 and 4 were engineered by substituting the structural genes, pre-membrane (prM) and envelope (E), of the dengue virus serotype 2 backbone with the prM and E genes of the DENV virus strains, DENV-1 16007, DENV-3 16562 or DENV-4 1036 virus, respectively. Thus, TDV is comprised of 4 dengue virus strains: dengue virus serotype 1 (live, attenuated), dengue virus serotype 2 (live, attenuated), dengue virus serotype 3 (live, attenuated), and dengue virus serotype 4 (live, attenuated). All 4 dengue virus serotypes are produced in Vero cells by recombinant deoxyribonucleic acid (DNA) technology. Dengue virus serotypes 1, 3, and 4 products contain genetically modified organisms. Specifically, genes of serotype-specific surface proteins are engineered into the dengue virus serotype 2 backbone.

Nonclinical studies carried out in mice and non-human primates have demonstrated a satisfactory safety, immunogenicity, and efficacy profile of TDV. Additionally, data from completed phase 1 and phase 2 clinical trials in humans have shown satisfactory reactogenicity, safety and immunogenicity profiles of TDV in healthy adults in non-endemic areas as well as in healthy adults and children in endemic areas in Asia and Latin America. Ongoing and completed phase 2 trials have enabled the selection of a final TDV dose (lyophilized formulation) and a 2-dose vaccination regimen (2 single doses) administered 3 months (ie, 90 days) apart by subcutaneous (SC) injection for use in the ongoing pivotal program. Results from an interim analysis for Part 1 of the phase 3 trial DEN-301 showed that the primary efficacy endpoint was met. In particular, the data demonstrated vaccine efficacy 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 (M4)]) until the end of Part 1.

The current investigator's brochure provides additional product information and a more detailed review of nonclinical studies and clinical trials.

Rationale for the Proposed Trial:

The WHO recommends that new vaccines should be introduced according to existing national immunization programs. Recombinant 9-valent human papillomavirus (HPV) vaccine is recommended in a 2-dose schedule 6 to 12 months apart in subjects 9 through 14 years of age. Further, if the second dose is administered earlier than 5 months after the first dose, then a third dose should be administered at least 4 months after the second dose.

Many similarities exist between the proposed vaccination schedule for TDV and the approved schedule for 9-valent HPV (9vHPV) vaccine, including the overlapping target age group and the potential delivery through school immunization programs.

In order to avoid barriers to the inclusion of TDV in routine national vaccination programs, the impact of TDV on vaccines administered via such programs needs to be examined. This is particularly relevant for low-income countries where the cost of a standalone vaccination could be too high, and potentially undermine TDV uptake, if inclusion in routine vaccine schedules were not possible.

With this trial, we aim to provide immunogenicity and safety data on the co-administration of 9vHPV vaccine with TDV in healthy subjects aged ≥9 to <15 years at the time of informed consent in order to facilitate inclusion into established vaccination schedules and mitigate the afore-mentioned problems. In this trial, approximately 614 subjects are planned to be enrolled.

The trial will be conducted in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) and good clinical practice (GCP) guidelines, and applicable regulatory requirements.

Trial Design:

This is a phase 3, open-label, randomized, multicenter trial in 614 healthy subjects aged ≥9 to <15 years in endemic areas for dengue, to investigate the immunogenicity and safety of the co-administration of TDV and 9vHPV vaccine vs 9vHPV vaccine alone. Subjects will be randomized equally to 1 of 2 groups (307 subjects per trial group):

- Group 1: first doses of 9vHPV vaccine + TDV co-administered on Day 1 (Month 0 [M0]), second dose of TDV

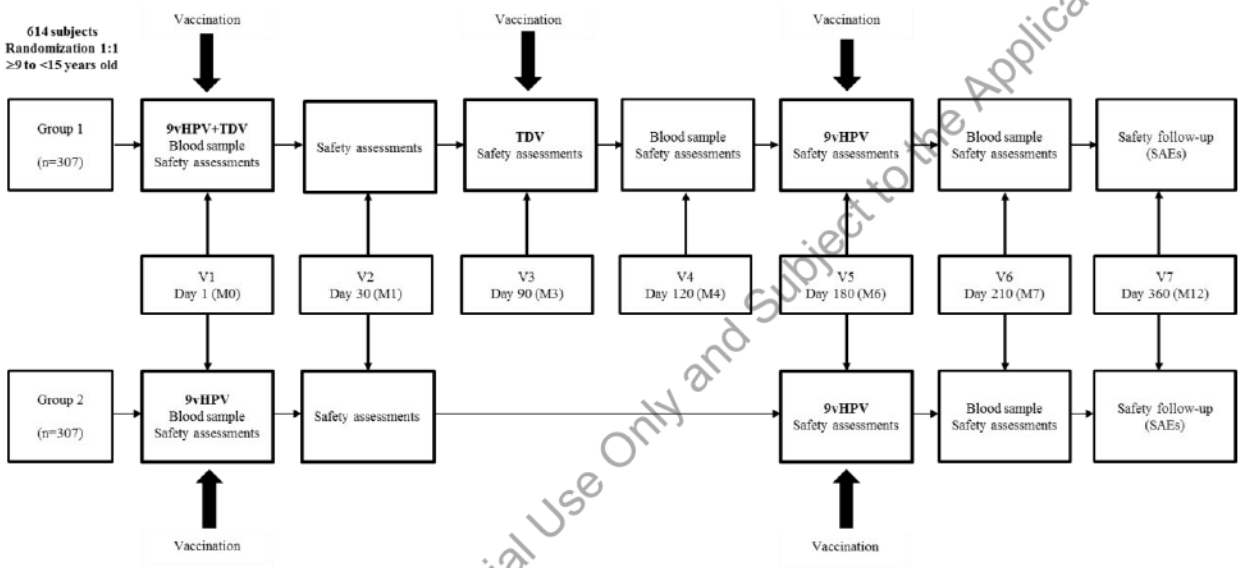
administered on Day 90 (M3), second dose of 9vHPV vaccine administered on Day 180 (M6).

- Group 2: first dose of 9vHPV vaccine administered on Day 1 (M0), second dose of 9vHPV vaccine administered on Day 180 (M6).

Concomitantly administered vaccines will be injected into opposite arms. All subjects will be followed-up for 6 months after the last trial vaccination, so the trial duration will be approximately 360 days (or 12 months) for each subject.

The schematic of the trial design and blood draw schedule is included as Figure 2.a.

Figure 2.a Schematic of Trial Design DEN-308



9vHPV, 9-valent human papillomavirus vaccine; M, month; n, number of subjects; SAEs, serious adverse events; TDV, tetravalent dengue vaccine candidate (live, attenuated); V, visit.

Immunogenicity evaluation

Blood samples for the measurement of HPV total immunoglobulin G (Merck assay) for both Groups 1 and 2 will be collected at pre-first vaccination (Day 1 [M0]) and at 1 month post-second 9vHPV vaccination (Day 210 [M7]).

Blood samples for the measurement of dengue neutralizing antibodies (by microneutralization test 50% [MNT_{50}]) will be collected for Group 1 only at pre-first vaccination (Day 1 [M0]) and at 1 month post-second TDV vaccination (Day 120 [M4]).

Safety evaluation

- Diary cards will be distributed to all subjects' legally authorized representatives (LARs) for the recording of:
  - Solicited local (injection site) reactions for 7 days following vaccination (day of vaccination+6 days) on Day 1 (M0) and Day 90 (M3). Collection starting on Day 1 (M0) will be for both injection sites and for subjects in Groups 1 and 2, and collection starting on Day 90 (M3) will only be for subjects in Group 1 after the second TDV dose.

    Reactions will include: injection site pain, injection site erythema and injection site swelling.
  - Solicited systemic adverse events (AEs) for 14 days following vaccination (day of vaccination+13 days) on Day 1 (M0) and Day 90 (M3). Collection starting on Day 1 (M0) will be for both injection sites and for subjects in Groups 1 and 2, and collection starting on Day 90 (M3) will only be for subjects in Group 1 after the second TDV dose.

    Events will include: (fever defined as body temperature ≥38.0°C [≥100.4°F]), asthenia, malaise, headache and

myalgia.

- Unsolicited AEs for 28 days following vaccination (day of vaccination+27 days) on Day 1 (M0) (Group 1 and 2) and Day 90 (M3) (Group 1).
- SAEs will be recorded for the trial duration (Group 1 and 2).

Data will be collected using an electronic Case Report Form (eCRF).

Primary Objective:

To demonstrate the non-inferiority (NI) of the immune response (in terms of geometric mean titers [GMTs]) to 2 doses of 9vHPV vaccine, 1 co-administered with TDV, compared with 2 doses of 9vHPV vaccine administered alone.

Secondary Objectives:

Immunogenicity

- To describe the immune response to HPV (in terms of seroresponse) in subjects administered 2 doses of 9vHPV vaccine, 1 co-administered with TDV, compared with subjects administered 2 doses of 9vHPV vaccine alone.
- To describe the immune response to TDV at 1 month following a second dose of TDV given 3 months after the first dose of TDV administered concomitantly with 9vHPV vaccine.

Safety

- To describe the safety profile after administration of TDV concomitantly with 9vHPV vaccine.

Subject Population:

Healthy Subjects: Yes

Age Range: ≥9 to <15 years at the time of informed consent (ie, from 9 years of age through to 14 years and 364 days of age before trial enrollment)

Planned Number of Subjects: 614

Planned Number of Trial Arms: 2 groups in a 1:1 ratio (307 subjects in each trial group).

Inclusion Criteria:

1. The subject is aged ≥9 to <15 years.
2. Male or female.
3. Subjects who are in good health at the time of entry into the trial as determined by medical history, physical examination (including vital signs), and the clinical judgment of the investigator.
4. The subject has signed and dated an assent form and/or parent(s) or LAR(s) have signed and dated a written informed consent form, including any required privacy authorization form, prior to the initiation of any trial procedures, after the nature of the trial has been explained according to local regulatory requirements.
5. Subjects who can comply with trial procedures and are available for the duration of follow-up.

Exclusion Criteria:

1. Subjects with an elevated oral temperature ≥38°C (≥100.4°F) within 3 days of the intended date of vaccination (consider whether applicable as an exclusion criterion or criterion for delay, see below).
2. Subjects with contraindications, warnings and/or precautions to vaccination with 9vHPV vaccine as specified within the prescribing information.
3. Known hypersensitivity or allergy to any of the trial vaccine components (including excipients of the trial vaccines).
4. Subjects with behavioral or cognitive impairment or psychiatric disease that, in the opinion of the investigator, may interfere with the subject's ability to participate in the trial.
5. Subjects with any history of progressive or severe neurologic disorder, seizure disorder or neuro-inflammatory disease (eg, Guillain-Barré syndrome).
6. Subjects with a history of or any current illness that, in the opinion of the investigator, might interfere with the

results of the trial or pose additional risk to the subjects due to participation in the trial.

7. Known or suspected impairment/alteration of immune function, including:
   a. Chronic use of oral steroids (equivalent to 20 mg/day prednisone ≥12 weeks/≥2 mg/kg body weight/day prednisone ≥2 weeks) within 60 days prior to Day 1 (M0) (use of inhaled, intranasal, or topical corticosteroids is allowed).
   b. Receipt of parenteral steroids (equivalent to 20 mg/day prednisone ≥12 weeks/≥2 mg/kg body weight/day prednisone ≥2 weeks) within 60 days prior to Day 1 (M0).
   c. Administration of immunoglobulins and/or any blood products within the 3 months prior to Day 1 (M0) or planned administration during the trial.
   d. Receipt of immunostimulants within 60 days prior to Day 1 (M0).
   e. Immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy within 6 months prior to Day 1 (M0).
   f. Human immunodeficiency virus (HIV) infection or HIV-related disease.
   g. Hepatitis B virus infection.
   h. Hepatitis C virus infection.
   i. Genetic immunodeficiency.
8. Abnormalities of splenic or thymic function.
9. Subjects with a known bleeding diathesis, or any condition that may be associated with a prolonged bleeding time.
10. Subjects with any serious chronic or progressive disease according to the judgment of the investigator (eg, neoplasm, hematologic malignancies, insulin dependent diabetes, cardiac, renal or hepatic disease).
11. Subjects participating in any clinical trial with another trial vaccine 30 days prior to Day 1 (M0) or intending to participate in another clinical trial at any time during the conduct of this trial.
12. Subjects who received any other vaccines within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to enrollment in this trial or who are planning to receive any vaccine within 28 days of trial vaccine administration.
13. Subjects who have used antipyretics and/or analgesic medications within 24 hours prior to vaccination. The reason for their use (prophylaxis versus treatment) must be documented. Trial entry should be delayed to allow for a full 24 hours to have passed since last use of antipyretics and/or analgesic medications.
14. Subjects involved in the trial conduct or their first-degree relatives.
15. Subjects with a history of substance or alcohol abuse within the past 2 years.
16. Subjects who are pregnant or breastfeeding.
17. Females of childbearing potential[1] who are sexually active and who have not used any of the acceptable contraceptive methods[2] for at least 2 months prior to Day 1 (M0).
18. Females of childbearing potential who are sexually active and who refuse to use an acceptable contraceptive method up to 6 weeks post-final vaccination on Day 180 (M6). In addition, they must be advised not to donate ova during this period.
19. Any positive or indeterminate pregnancy test.

[1] Defined as status post onset of menarche and not meeting any of the following conditions: bilateral tubal ligation (at least 1 year previously), bilateral oophorectomy (at least 1 year previously) or hysterectomy.
[2] One or more of the following: hormonal contraceptive (such as oral, injection, transdermal patch, implant, cervical ring), intrauterine device, monogamous relationship with vasectomized partner (partner must have been vasectomized for at least 6 months prior to Day 1 [M0]). Other contraceptive methods may be considered in agreement with the Sponsor and will be approved by the appropriate ethics committee.

20. Previous and planned vaccination (during the trial conduct), against any flavivirus (except Japanese encephalitis [JE]) including dengue, yellow fever (YF) viruses or tick-borne encephalitis.
21. Previous and planned vaccination (during the trial conduct) against HPV.
22. Previous participation in any clinical trial of a dengue or other flavivirus (eg, West Nile [WN] virus) candidate vaccine, except for subjects who received placebo in those trials.
23. Subjects with a current or previous infection with a flavivirus such as Zika, YF, JE, WN fever, tick-borne encephalitis or Murray Valley encephalitis.

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

Criteria for delay of second trial vaccine administration at Day 90 (M3) or Day 180 (M6):

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

If any of the criteria below occur at the time scheduled for the trial vaccine administration at Day 90 (M3) or Day 180 (M6), the subsequent dose may be administered at a later date as long as the subject is otherwise eligible to continue trial participation. In certain situations, the period of delay may lead to deviation from the time window for the subsequent dose. The decision to vaccinate in those situations will be made by the investigator.

The following clinical circumstances warrant a delay in the administration of trial vaccine at Day 90 (M3) or Day 180 (M6):

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

Contraindications to trial vaccine administration at Day 90 (M3) or Day 180 (M6):

There are also circumstances under which receipt of the trial vaccination at Day 90 (M3) or Day 180 (M6) is contraindicated in this trial. These circumstances include but are not limited to anaphylaxis or severe hypersensitivity reactions following the administration of an earlier trial vaccination at Day 1 (M0) or Day 90 (M3), respectively. If these reactions occur, the subject must not receive the trial vaccination at Day 90 (M3) or Day 180 (M6), respectively, but will be encouraged to continue trial participation for safety follow-up.

Trial Vaccines:

Investigational vaccine

The investigational vaccine, TDV, is a Dengue Tetravalent Vaccine (Live, Attenuated) comprised of a molecularly characterized, attenuated dengue serotype 2 strain (TDV-2), a dengue serotypes 2/1 recombinant strain (TDV-1), a dengue serotypes 2/3 recombinant strain (TDV-3), and a dengue serotypes 2/4 recombinant strain (TDV-4) with potencies of not less than 3.3, 2.7, 4.0 and 4.5 $\log_{10}$ plaque forming units per dose of TDV-1, TDV-2, TDV-3, and TDV-4, respectively. TDV is a lyophilized vaccine that will be reconstituted in diluent (37 mM NaCl solution) prior to administration.

9vHPV vaccine

The 9vHPV vaccine (Merck) is a recombinant 9-valent vaccine containing the L1 proteins for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. The 9vHPV vaccine contains yeast protein, and the vaccine antigen is adsorbed on an aluminum-containing adjuvant. Each dose of 9vHPV vaccine is 0.5 mL and is supplied as a single-dose vial or in prefilled syringes that do not contain latex.

Route of administration

TDV will be administered by the SC route, 9vHPV vaccine will be administered by the intramuscular (IM) route.

Duration of the Trial and Subject Participation:

The trial duration for each subject will be approximately 360 days or 12 months.

Criteria for Evaluation and Analyses:

Primary endpoint:

- Geometric mean titers (GMTs) for HPV Types 6, 11, 16, 18, 31, 33, 45, 52, 58 on Day 210 (M7).

Secondary endpoints:

Immunogenicity

- Seropositivity rates (% of subjects seropositive) for HPV Types 6, 11, 16, 18, 31, 33, 45, 52 and 58 on Day 210 (M7) as measured by immunoglobulin G binding assay (IgGBA) or equivalent assay.
- GMTs of neutralizing antibodies (by MNT_{50}) for each of the 4 dengue serotypes on Day 120 (M4).
- Seropositivity rates (% of subjects seropositive) for each of the 4 dengue serotypes and for multiple (2, 3 or 4) dengue serotypes on Day 120 (M4).

Definition of seropositivity - Dengue virus

Seropositivity is defined as a reciprocal neutralizing antibody titer ≥10 for any of the 4 dengue serotypes.

Definition of seropositivity - HPV

The minimum anti-HPV titer that confers protective efficacy has not been determined.

Seropositivity for HPV is defined as an anti-HPV titer greater than or equal to the pre-specified serostatus cut-off for a given HPV type. Seronegativity is defined as an anti-HPV titer less than the pre-specified serostatus cut-off for a given HPV type. The serostatus cut-off is the antibody titer level above the assay's lower limit of quantification that reliably distinguishes sera samples classified by clinical likelihood of HPV infection and positive or negative status by previous versions of IgGBA or equivalent assay.

Serum antibodies to HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 will be measured with an IgGBA or equivalent assay. Titers will be reported in milli-Merck units/mL with the use of the IgGBA. For the lower limits of quantification and serostatus cut-offs for each of the 9 vaccine HPV types, please refer to the statistical analysis plan (SAP).

Safety

- Frequency and severity of solicited local (injection site) reactions for 7 days (day of vaccination+6 days) (Group 2 and collected at each injection site in Group 1) and solicited systemic AEs for 14 days (day of vaccination+13 days) after vaccination on Day 1 (M0) (Group 1 and 2) and Day 90 (M3) (Group 1).
- Percentage of subjects with any unsolicited AEs for 28 days (day of vaccination+27 days) after vaccination on Day 1 (M0) (Group 1 and 2) and Day 90 (M3) (Group 1).
- Percentage of subjects with SAEs throughout the trial (Group 1 and 2).

Statistical Considerations:

Analysis sets

Safety set: the safety set will consist of all subjects who received at least 1 dose of TDV or 9vHPV.

Full analysis set (FAS): the FAS will include all randomized subjects who received at least 1 dose of trial vaccine and

for whom valid pre-dosing (Day 0 [M0]) and at least 1 post-dosing measurement have been received for immunogenicity assessments.

Per-protocol set (PPS): the PPS will exclude all subjects seropositive for HPV at Baseline and will include all subjects in the FAS who have no major protocol violations. The major protocol violation criteria will be defined as part of a data review prior to the analysis. The categories of major protocol violations include: (1) not meeting selected entry criteria, (2) receiving the wrong trial vaccine, (3) receiving prohibited therapies, and (4) other major protocol violations that may be identified during data reviews.

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

Analysis of demographics and other baseline characteristics

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

Immunogenicity analysis

The primary objective, NI of the immune response to 2 doses of 9vHPV vaccine when concomitantly administered with TDV compared to administration of 9vHPV vaccine alone, will be assessed in terms of GMTs on Day 210 (M7). NI for each HPV type will be concluded if the upper bound of the 95% confidence interval (CI) for the GMT ratio (Group 2/Group 1) is less than the NI margin of 1.5. Overall NI will be concluded if NI requirement is met for all 9 HPV types, therefore no multiplicity adjustment of first type error is needed and 95% CI will be used in each comparison.

Descriptive statistics including 95% CI for the primary and secondary endpoints, including seropositivity rates and GMTs, will be computed by trial group for all available assays at all relevant time points.

An analysis of (co)variance (AN[CO]VA) model on the natural logarithms of titer values will be used to compute the 95% CI of the GMT ratios, with trial group as a factor based on the PPS. A similar, supportive ANCOVA, with trial group and the natural logarithms of pre-vaccination titers as factors may be provided based on the FAS.

Handling of missing data will be described in the SAP.

Safety analysis

Solicited AEs

Presence and severity (Grade) of solicited local (injection site reactions pain, injection site erythema and injection site swelling) will be collected using diary cards on Day 1 (M0) and Day 90 (M3) for 7 days following each vaccination. In Group 1, reactions at both injection sites (TDV and 9vHPV vaccine) will be collected on Day 1 (M0) and at the TDV injection site on Day 90 (M3). In Group 2, reactions at the 9vHPV vaccine injection site will be collected on Day 1 (M0).

Presence and severity (Grade) of solicited systemic AEs (fever, asthenia, malaise, headache and myalgia) will be collected using diary cards on Day 1 (M0) and Day 90 (M3) for 14 days following each vaccination. Collection starting on Day 1 (M0) will be for both injection sites and for subjects in Groups 1 and 2, and collection starting on Day 90 (M3) will only be for subjects in Group 1 after the second TDV dose.

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

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

Unsolicited AEs

Unsolicited AEs will be assessed for 28 days following trial vaccination (day of vaccination+27 days).
Unsolicited AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), and summarized by Preferred Term (PT) and System Organ Class (SOC) for each trial group.

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

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

SAEs

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

Sample Size Justification:

The sample size calculation assumes a significance level of 0.025 (one-sided).

For the primary objective of showing NI of 9vHPV GMTs, the calculation assumes a NI margin of 1.5, a true GMT ratio of 1 between trial groups at Day 210 (M7), and that the natural logarithms of the antibody titers against 9 HPV types are independent normally distributed with standard deviations of 0.95, 0.86, 0.98, 0.91, 0.98, 0.94, 1.09, 1.03, and 0.94. The largest variability 1.09 was assumed and used for sample size calculations for all 9 strains.

A sample size of 307 subjects per group, with approximately 261 evaluable subjects per trial group (adjusted for approximately 15% subjects not evaluable for the immunogenicity assessments), is sufficient to achieve approximately 90% power for showing NI for the primary objective.
Sample size calculations were performed using nQuery Advisor® 8.

Interim Analysis:

An interim analysis of immunogenicity and safety data is planned when all subjects have completed the Day 210 (M7) visit. This will be reported in an interim clinical study report (CSR). A final CSR will be prepared upon trial completion to include safety data collected up to the end of the trial on Day 360 (M12) and will also include results for the whole trial duration.

Data Monitoring Committee (DMC):

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

DEN-308 Version 5.0 (3 March 2021)

2.1 Schedule of Trial Procedures

Table 2.a Schedule of Trial Procedures (Visits 1 to 7 [Day 1 (M0) to Day 360 (M12)])

Visits		**1**	**2**	**3**	**4**	**5**	**6**	**7**
Day		**Day 1**	**Day 30**	**Day 90**	**Day 120**	**Day 180**	**Day 210**	**Day 360**
Month		**M0**	**M1**	**M3**	**M4**	**M6**	**M7**	**M12 (ET) [a]**
Visit window (days)		**1±NA**	**30 days (-1/+7) after Visit 1**	**90 days (-15/+25) after Visit 1**	**30 days (-1/+7) after Visit 3**	**90 days (-15/+25) after Visit 3**	**30 days (-1/+7) after Visit 5**	**180 days (-7/+14) after Visit 5**
Procedures								
Signed informed consent/pediatric assent		X						
Assessment of eligibility criteria		X						
Review of systems		X						X
Demographics, medical history, prior medications/vaccinations		X						
Concomitant medications/vaccinations [b]		X	X	X [d]	X [d]	X	X	X
Complete physical examination [c]		X		X [d]		X		
Targeted physical examination [e]			X		X [d]		X	X
Vital signs [f]		X	X	X [d]	X [d]	X	X	X
Pregnancy test (urine) [g]		X		X [d]		X		
Pregnancy avoidance guidance [h]		X	X	X [d]	X [d]	X	X	
Randomization		X						
Check criteria for delay of trial vaccine administration	Group 1			X		X		
	Group 2					X		
Check contraindications for trial vaccine administration	Group 1	X		X		X		
	Group 2	X				X		
Blood collection for immunogenicity testing [i]	Group 1 – Dengue neutralizing antibodies (5 mL)	X			X			
	Group 1 – HPV neutralizing antibodies (5 mL)	X					X	

Visits		**1**	**2**	**3**	**4**	**5**	**6**	**7**
Day		**Day 1**	**Day 30**	**Day 90**	**Day 120**	**Day 180**	**Day 210**	**Day 360**
Month		**M0**	**M1**	**M3**	**M4**	**M6**	**M7**	**M12 (ET) [a]**
	Group 2 – HPV neutralizing antibodies (5 mL)	X					X	
Vaccination with TDV		X [d]		X [d]				
Vaccination with 9vHPV vaccine		X				X		
Post-vaccination observation [j]	TDV vaccine	X [d]		X [d]				
	9vHPV vaccine	X				X		
Diary card distribution [k]	Group 1	X		X				
	Group 2	X						
Diary card review/collection of solicited local (injection site) reactions and systemic AEs	Group 1		X		X			
	Group 2		X					
AEs [l]		X	X	X [d]	X [d]			
SAEs, AEs leading to IP withdrawal or trial discontinuation [m]		X	X	X	X	X	X	X

Note: 9vHPV=Recombinant 9-valent human papillomavirus vaccine; AE=adverse event, ET=early termination, M=month, SAE=serious adverse event, TDV=Dengue Tetravalent Vaccine (Live, Attenuated); V=visit.
Note: when a site visit cannot be carried out due to the coronavirus disease 2019 (COVID-19) pandemic, alternative methods of contact (e.g telephone contact) will be made for subjects who are still under monitoring for safety reporting.
Footnotes:

a) The final (end of trial) visit will be performed on Day 360 (M12). If a subject terminates earlier, the final (end of trial) visit procedures should be performed at their last trial visit, if possible. For all subjects receiving trial vaccine(s), the investigator must complete the "End of Trial" eCRF page.
b) All medications and vaccine history from 1 month (minimum 28 days) prior to administration of each dose of trial vaccine(s) up to 1 month (minimum 28 days) thereafter, steroids and immunostimulants within 60 days prior to Day 1 (M0), immunoglobulins and blood products within 3 months prior to Day 1 (M0), and immunosuppressive therapy within 6 months prior to Day 1 (M0).
c) Physical examination including measurement of weight and height; body mass index will be calculated automatically.
d) Only applicable for subjects in Group 1.
e) Subjects may undergo a brief symptom-directed physical examination. Clinically significant changes from the baseline examination should be recorded in the subject's source documents and eCRF.
f) Vital signs including (but not limited to) the measurement of systolic blood pressure/diastolic blood pressure, heart rate, and body temperature.
g) For female subjects of childbearing potential, a pregnancy test will be performed after informed consent and pediatric assent is obtained.

h) Female subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy and donation of ova. Subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the trial procedures, and female subjects of childbearing potential who are sexually active will be reminded during trial visits to adhere to acceptable contraceptive methods up to 6 weeks after the last dose of 9vHPV (Day 180 [M6]) + 6 weeks).

i) The blood sample on Day 1 (M0) should be taken prior to trial vaccination. The blood sample on Day 120 (M4) and Day 210 (M7) for Group 1 should be taken at least 29 days after the trial vaccine vaccination on Day 90 (M3) and Day 180 (M6), respectively, and the blood sample on Day 210 (M7) for Group 2 should be taken at least 29 days after the trial vaccine vaccination on Day 180 (M6).

j) After each trial vaccination, TDV and/or 9vHPV vaccine (Group 1 and 2) on Day 1 (M0), the second dose of TDV on Day 90 (M3) (Group 1) and the second dose of 9vHPV (Group 1 and 2) on Day 180 (M6), the subject will be observed for at least 30 minutes including observation for solicited local (injection site) reactions, solicited systemic AEs (including body temperature measurement), and unsolicited AEs.

k) Diary (paper or electronic) cards will be used for the collection of:
    1. Solicited local (injection site) reactions for 7 days after TDV and 9vHPV trial vaccination (day of vaccination + 6 days) on Day 1 (M0) and Day 90 (M3). Collection starting on Day 1 (M0) will be for both injection sites and for subjects in Groups 1 and 2, and collection starting on Day 90 (M3) will only be for subjects in Group 1 after the second TDV dose. If solicited local AEs continue on Day 8 following each trial vaccination (on Day 1 (M0) [Group 1 and 2] and on Day 90 (M3) [Group 1 only]), record the extended information on the Adverse Event eCRF.
    2. Solicited systemic AEs for 14 days after TDV and 9vHPV trial vaccination (the day of vaccination + 13 days) on Day 1 (M0) and Day 90 (M3). Collection starting on Day 1 (M0) will be for both injection sites and for subjects in Groups 1 and 2, and collection starting on Day 90 (M3) will only be for subjects in Group 1 after the second TDV dose. If solicited systemic AEs continue on Day 15 following each trial vaccination (on Day 1 (M0) [Group 1 and 2] and on Day 90 (M3) [Group 1 only]), record the extended information on the Adverse Event eCRF. The investigator will categorize events by severity (mild, moderate or severe) and will assess causality to vaccine administration for solicited systemic AEs (related or not related).

l) Unsolicited AEs (non-serious and serious) for 28 days (including the day of vaccination) after TDV and the first 9vHPV vaccination will be collected by interview and recorded for all subjects on Day 1 (M0), Day 30 (M1), Day 90 (M3) and Day 120 (M4). The investigator will categorize events by severity (mild, moderate or severe) and will assess causality to vaccine administration (related or not related).

m) AEs leading to discontinuation or withdrawal will be collected for the trial duration. SAEs will be collected from the time the subject is administered the trial vaccine(s) (Day 1 [M0]) up to Day 360 (M12). SAEs will be reported to the sponsor within 24 hours of the investigator becoming aware of the event.

3.0 TRIAL REFERENCE INFORMATION

3.1 Trial-Related Responsibilities

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

3.2 Principal Investigator/Coordinating Investigator

Selection criteria for the principal investigator (PI) 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 a signatory investigator from the investigators who participate in the study. The signatory investigator will be required to review and sign the clinical protocol. The signatory investigator will also be required to review and sign the clinical study report (CSR) and by doing so agrees that it accurately describes the results of the trial.

3.3 List of Abbreviations

9vHPV	Recombinant 9-valent human papillomavirus vaccine
AE	Adverse event
ANCOVA	Analysis of covariance
CI	Confidence interval
COVID-19	Coronavirus disease 2019
CSR	Clinical study report
CYD-TDV	Chimeric yellow fever virus-dengue virus tetravalent dengue vaccine
DENV	Wild type dengue virus
DENV-1, -2, -3, -4	Wild type dengue virus serotypes 1, 2, 3, and 4
DHF	Dengue hemorrhagic fever
DMC	Data Monitoring Committee
DSS	Dengue shock syndrome
E	Envelope
ECG	Electrocardiogram
eCRF	Electronic case report form
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good clinical practice
GMT	Geometric mean titer
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
IB	Investigator's brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IgGBA	Immunoglobulin G binding assay
IM	Intramuscular
IRB	Institutional Review Board
IRT	Interactive response technology
JE	Japanese encephalitis
LAR	Legally authorized representative
M	Month
MedDRA	Medical Dictionary for Regulatory Activities
MHRA	Medicines and Healthcare Products Regulatory Agency of United Kingdom
MNT_{50}	Microneutralization test 50%
NI	Non-inferiority
PDK	Primary dog kidney
PI	Principal investigator
PIP	Pediatric investigation plan
PMDA	Pharmaceuticals and Medical Devices Agency of Japan

PPS	Per-protocol set
prM	Pre-membrane
PT	Preferred term
QTL	Quality tolerance limits
SAE	Serious adverse event
SAGE	Strategic Advisory Group of Experts on Immunization
SAP	Statistical analysis plan
SC	Subcutaneous
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TDV	Dengue Tetravalent Vaccine (Live, Attenuated), also known as TAK-003
TDV-1	Dengue serotypes 2/1 recombinant strain
TDV-2	Molecularly characterized, attenuated dengue serotype 2 strain
TDV-3	Dengue serotypes 2/3 recombinant strain
TDV-4	Dengue serotypes 2/4 recombinant strain
WHO	World Health Organization
WN	West Nile
YF	Yellow fever

3.4 Corporate Identification

TV Takeda Vaccines, Inc.

4.0 INTRODUCTION

4.1 Background

Dengue fever is caused by infection with the wild type dengue virus (DENV), a ribonucleic acid virus that occurs as 4 recognized serotypes, DENV-1, DENV-2, DENV-3, or DENV-4. These dengue viruses are transmitted to human by mosquitoes (primarily *Aedes aegypti*) and are endemic in Asia, Central and South America, the Caribbean, the Pacific Islands, and parts of Africa. There are an estimated 390 million dengue infections per year worldwide, which is more than 3 times the previous World Health Organization (WHO) estimate of 50 to 100 million cases [3]. Every year, around 500,000 cases of dengue hemorrhagic fever (DHF) require hospitalization with an estimated death rate of 2.5%, primarily in children. It is estimated that 3.9 billion people are at risk of dengue infection [4-7].

Dengue fever is clinically defined as an acute febrile illness with 2 or more of the following manifestations: headache, retro-orbital pain, myalgia, arthralgia, rash, hemorrhagic manifestations, or leukopenia, and occurrence at the same location and time as other confirmed cases of dengue fever. The most severe forms of dengue infection – DHF and dengue shock syndrome (DSS) – are life threatening. Primary infection with any one of the 4 dengue serotypes is thought to result in life-long protection from re-infection by the same serotype, but does not protect against a secondary infection by one of the other 3 dengue serotypes and may lead to an increased risk of severe disease (DHF/DSS) [6-9].

Treatment of dengue fever is based solely on signs and symptoms, with fluid replacement required for hemorrhagic or shock cases. An antiviral therapy for DENV infection is not yet 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 [4-10]. 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 [11] 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 [12]. 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 [13]. 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 [14].

Hence, there is a continued unmet public health need for safer and more efficacious dengue vaccines [15].

Dengue Tetravalent Vaccine (Live, Attenuated) (TDV) - Background:

The investigational vaccine TDV, also known as TAK-003, consists of 1 molecularly characterized, attenuated dengue virus serotype 2 strain denoted as the dengue virus serotype 2 backbone and 3 recombinant dengue virus strains expressing surface antigens corresponding to DENV serotypes 1-4. The dengue virus serotype 2 backbone is based upon the attenuated laboratory-derived DENV-2 virus strain, originally isolated at Mahidol University, Bangkok, Thailand and generated by 53 serial passages in primary dog kidney (PDK) cells (DENV-2 PDK-53) [16]. The recombinant, attenuated vaccine strains for dengue serotypes 1, 3 and 4 were engineered by substituting the structural genes, pre-membrane (prM) and envelope (E), of the dengue virus serotype 2 backbone with the prM and E genes of the DENV virus strains, DENV-1 16007, DENV-3 16562 or DENV-4 1036 virus, respectively [17]. Thus, TDV is comprised of 4 dengue virus strains: dengue virus serotype 1 (live, attenuated), dengue virus serotype 2 (live, attenuated), dengue virus serotype 3 (live, attenuated), and dengue virus serotype 4 (live, attenuated). All 4 dengue virus serotypes are produced in Vero cells by recombinant deoxyribonucleic acid (DNA) technology. Dengue virus serotypes 1, 3, and 4 products contain genetically modified organisms. Specifically, genes of serotype-specific surface proteins are engineered into the dengue virus serotype 2 backbone.

Nonclinical studies carried out in mice and nonhuman primates have demonstrated a satisfactory safety, immunogenicity, and efficacy profile of TDV. Additionally, data from completed phase 1 and phase 2 clinical trials in humans have shown satisfactory reactogenicity, safety and immunogenicity profiles of TDV in healthy adults in non-endemic areas as well as in healthy adults and children in endemic areas in Asia and Latin America. Ongoing and completed phase 2 clinical trials have enabled the selection of a final TDV dose (lyophilized formulation), and a 2-dose vaccination regimen (2 single doses) administered 3 months (ie, 90 days) apart by subcutaneous (SC) injection for use in the ongoing pivotal program. Results from an interim analysis for Part 1 of the phase 3 trial DEN-301 showed that the primary efficacy endpoint was met. In particular, the data demonstrated vaccine efficacy 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 (M4)]) until the end of Part 1.

The current investigator's brochure (IB) provides additional product information and a more detailed review of nonclinical studies and clinical trials.

4.2 Rationale for the Proposed Trial

The WHO recommends that new vaccines should be introduced according to existing national immunization programs [18]. Recombinant 9-valent human papillomavirus (HPV) vaccine is recommended in a 2-dose schedule 6 to 12 months apart in subjects 9 through 14 years of age. Further, if the second dose is administered earlier than 5 months after the first dose, then a third dose should be administered at least 4 months after the second dose [19].

Many similarities exist between the proposed vaccination schedule for TDV and the approved schedule for 9-valent HPV (9vHPV) vaccine, including the overlapping target age group and the potential delivery through school immunization programs.

In order to avoid barriers to the inclusion of TDV in routine national vaccination programs, the impact of TDV on vaccines administered via such programs needs to be examined. This is particularly relevant for low-income countries where the cost of a standalone vaccination could be too high, and potentially undermine TDV uptake, if inclusion in routine vaccine schedules were not possible.

With this trial, we aim to provide immunogenicity and safety data on the co-administration of 9vHPV vaccine with TDV in healthy subjects aged ≥9 to <15 years at the time of informed consent in order to facilitate inclusion into established vaccination schedules and mitigate the afore-mentioned problems. In this trial, approximately 614 subjects are planned to be enrolled.

The trial will be conducted in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) E6 (R2), and Good Clinical Practice (GCP) guidelines [2], and applicable regulatory requirements [1].

5.0 TRIAL OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 Primary Objective

To demonstrate the non-inferiority (NI) of the immune response (in terms of geometric mean titers [GMTs]) to 2 doses of 9vHPV vaccine, 1 co-administered with TDV, compared with 2 doses of 9vHPV vaccine administered alone.

5.1.2 Secondary Objectives

Immunogenicity

- To describe the immune response to HPV (in terms of seroresponse) in subjects administered 2 doses of 9vHPV vaccine, 1 co-administered with TDV, compared with subjects administered 2 doses of 9vHPV vaccine alone.
- To describe the immune response to TDV at 1 month following a second dose of TDV given 3 months after the first dose of TDV administered concomitantly with 9vHPV vaccine.

Safety

- To describe the safety profile after administration of TDV concomitantly with 9vHPV vaccine.

5.2 Endpoints

5.2.1 Primary Endpoint

- Geometric mean titers for HPV Types 6, 11, 16, 18, 31, 33, 45, 52, 58 on Day 210 (Month 7 [M7]).

5.2.2 Secondary Endpoints

Immunogenicity

- Seropositivity rates (% of subjects seropositive) for HPV Types 6, 11, 16, 18, 31, 33, 45, 52 and 58 on Day 210 (M7) as measured by immunoglobulin G binding assay (IgGBA) or equivalent assay.
- GMTs of neutralizing antibodies (by microneutralization test 50% [MNT_{50}]) for each of the 4 dengue serotypes on Day 120 (M4).
- Seropositivity rates (% of subjects seropositive) for each of the 4 dengue serotypes and for multiple (2, 3 or 4) dengue serotypes on Day 120 (M4).

Definition of seropositivity - dengue virus

Seropositivity is defined as a reciprocal neutralizing antibody titer ≥10 for any of the 4 dengue serotypes.

Definition of seropositivity - HPV

The minimum anti-HPV titer that confers protective efficacy has not been determined.

Seropositivity for HPV is defined as an anti-HPV titer greater than or equal to the pre-specified serostatus cut-off for a given HPV type. Seronegativity is defined as an anti-HPV titer less than the pre-specified serostatus cut-off for a given HPV type. The serostatus cut-off is the antibody titer level above the assay's lower limit of quantification that reliably distinguishes sera samples classified by clinical likelihood of HPV infection and positive or negative status by previous versions of IgGBA or equivalent assay.

Serum antibodies to HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58 will be measured with an IgGBA or equivalent assay. Titers will be reported in milli-Merck units/mL with the use of the IgGBA. For the lower limits of quantification and serostatus cut-offs for each of the 9 vaccine HPV types, please refer to the statistical analysis plan (SAP).

Safety

- Frequency and severity of solicited local (injection site) reactions for 7 days (day of vaccination+6 days) (Group 2 and collected at each injection site in Group 1) and solicited systemic adverse events (AEs) for 14 days (day of vaccination+13 days) after vaccination on Day 1 (M0) (Group 1 and 2) and Day 90 (M3) (Group 1).
- Percentage of subjects with any unsolicited AEs for 28 days (day of vaccination+27 days) after vaccination on Day 1 (M0) (Group 1 and 2) and Day 90 (M3) (Group 1).
- Percentage of subjects with serious AEs (SAEs) throughout the trial (Group 1 and 2).

6.0 TRIAL DESIGN AND DESCRIPTION

6.1 Trial Design

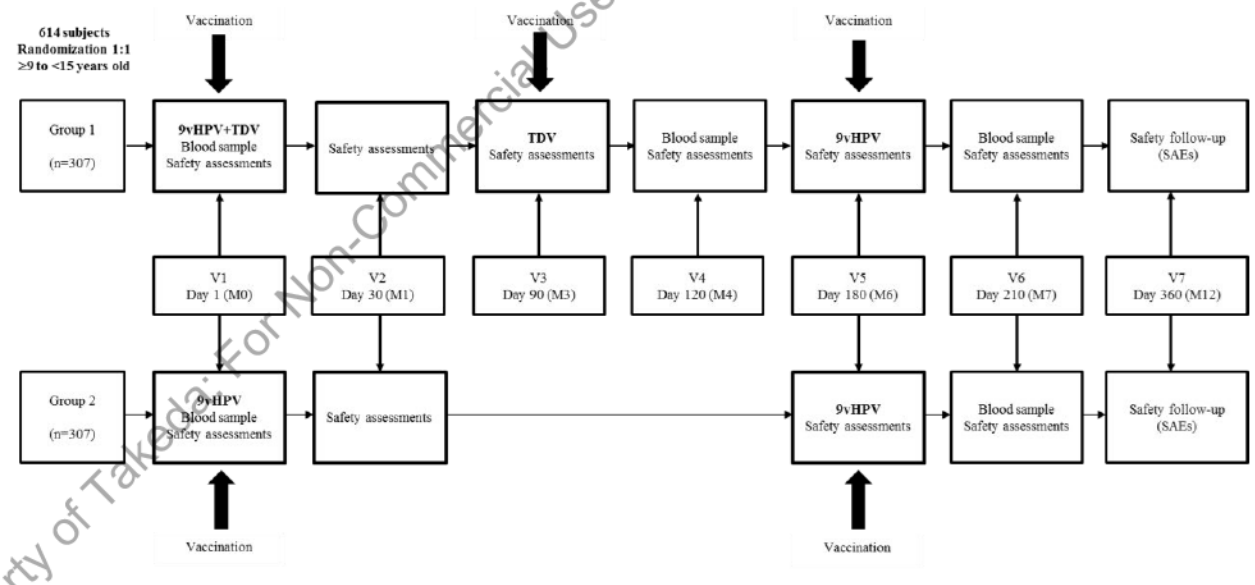
This is a phase 3, open-label, randomized, multicenter trial in 614 healthy subjects aged ≥9 to <15 years in endemic areas for dengue, to investigate the immunogenicity and safety of the co-administration of TDV and 9vHPV vaccine vs 9vHPV vaccine alone. Subjects will be randomized equally to 1 of 2 groups (307 subjects per trial group):

- Group 1: first doses of 9vHPV vaccine + TDV co-administered on Day 1 (M0), second dose of TDV administered on Day 90 (M3), second dose of 9vHPV vaccine administered on Day 180 (M6)
- Group 2: first dose of 9vHPV vaccine administered on Day 1 (M0), second dose of 9vHPV vaccine administered on Day 180 (M6)

Concomitantly administered vaccines will be injected into opposite arms. All subjects will be followed-up for 6 months after the last trial vaccination, so the trial duration will be approximately 360 days (or 12 months) for each subject.

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

Figure 6.a Schematic of Trial Design DEN-308



9vHPV, 9-valent human papillomavirus vaccine; M, month; n, number of subjects; SAEs, serious adverse events; TDV, tetravalent dengue vaccine candidate (live, attenuated); V, visit.

Immunogenicity evaluation

Blood samples for the measurement of HPV total immunoglobulin G (Merck assay) for both Groups 1 and 2 will be collected at pre-first vaccination (Day 1 [M0]) and at 1 month post-second 9vHPV vaccination (Day 210 [M7]).

Blood samples for the measurement of dengue neutralizing antibodies (by MNT_{50}) will be collected for Group 1 only at pre-first vaccination (Day 1 [M0]) and at 1 month post-second TDV vaccination (Day 120 [M4]).

Safety evaluation

Diary cards will be distributed to all subjects' legally authorized representatives (LAR) for the recording of:

- Solicited local (injection site) reactions for 7 days following vaccination (day of vaccination+6 days) on Day 1 (M0) (Group 2 and collected at each injection site in Group 1) and Day 90 (M3) (Group 1).

  Reactions 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) on Day 1 (M0) (Group 1 and 2) and Day 90 (M3) (Group 1).

  Events will include: (fever defined as body temperature ≥38.0°C [≥100.4°F]) [20], asthenia, malaise, headache and myalgia.

- Unsolicited AEs for 28 days following vaccination (day of vaccination+27 days) on Day 1 (M0) (Group 1 and 2) and Day 90 (M3) (Group 1).

- SAEs will be recorded for the trial duration (Group 1 and 2).

Data will be collected using an electronic Case Report Form (eCRF).

6.2 Justification for Trial Design, Dose, and Endpoints

The trial design and the collection of solicited AEs (local [injection site] reactions and systemic AEs), and unsolicited AEs (serious and non-serious) following trial dose administration are consistent with vaccine evaluation trials.

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

The trial is open label given that the main purpose of the trial is to investigate immunological interference for the co-administered trial vaccines where blinding is less relevant than for safety assessments. Furthermore, the sample size of the trial is considered too small to detect safety issues and thus does not support a blinded design for the current trial. Notably, the safety profile of the licensed 9vHPV vaccine is well known and for TDV a satisfactory safety profile has been seen in completed phase 2 and phase 3 trials.

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

The age range for 9vHPV vaccine administration is according to the approved prescribing information and WHO recommendations. The trial population selected to receive either or both TDV and 9vHPV vaccines in this trial has been thus selected because this age group is the most likely to receive 9vHPV vaccine according to the vaccine label and the WHO, and it is important to incorporate this into existing vaccination schedules [18,19].

Blood sampling volumes and the planned schedule are consistent with the recommendations regarding blood sampling in children and adolescents from 9 to 15 years [21,22].

Details relating to the sample size are presented in Section 13.3. The rationale for the proposed trial is given in Section 4.2. Trial endpoints are detailed in Section 5.2. The current IB contains additional information and a more detailed review of non-clinical studies and clinical trials.

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

The trial duration for each subject will be approximately 360 days (or 12 months) including trial dose administration (Day 1 [M0], Day 90 [M3] and Day 180 [M6] and follow-up through Day 360 [M12]).

6.4 Premature Termination or Suspension of Trial or Investigational Site

6.4.1 Criteria for Premature Termination or Suspension of the Trial

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

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

6.4.2 Criteria for Premature Termination or Suspension of Investigational Sites

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

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

In the event that the sponsor, an Institutional Review Board (IRB)/Independent Ethics Committee (IEC) or regulatory authority elect to terminate or suspend the trial or the participation of an investigational site, a trial-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable investigational sites during the course of termination or trial suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

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

7.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria:

1. The subject is aged ≥9 to <15 years.
2. Male or female.
3. Subjects who are in good health at the time of entry into the trial as determined by medical history, physical examination (including vital signs), and the clinical judgment of the investigator.
4. The subject has signed and dated an assent form and/or parent(s) or LAR(s) have signed and dated a written informed consent form, including any required privacy authorization form, prior to the initiation of any trial procedures, after the nature of the trial has been explained according to local regulatory requirements.
5. Subjects who can comply with trial procedures and are available for the duration of follow-up.

7.2 Exclusion Criteria

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

1. Subjects with an elevated oral temperature ≥38°C (≥100.4°F) within 3 days of the intended date of vaccination (consider whether applicable as an exclusion criterion or criterion for delay, see Section 7.3).
2. Subjects with contraindications, warnings and/or precautions to vaccination with 9vHPV vaccine as specified within the prescribing information.
3. Known hypersensitivity or allergy to any of the trial vaccine components (including excipients of the trial vaccines).
4. Subjects with behavioral or cognitive impairment or psychiatric disease that, in the opinion of the investigator, may interfere with the subject's ability to participate in the trial.
5. Subjects with any history of progressive or severe neurologic disorder, seizure disorder or neuro-inflammatory disease (eg, Guillain-Barré syndrome).
6. Subjects with a history of or any current illness that, in the opinion of the investigator, might interfere with the results of the trial or pose additional risk to the subjects due to participation in the trial.
7. Known or suspected impairment/alteration of immune function, including:
   a) Chronic use of oral steroids (equivalent to 20 mg/day prednisone ≥12 weeks/≥2 mg/kg body weight/day prednisone ≥2 weeks) within 60 days prior to Day 1 (M0) (use of inhaled, intranasal, or topical corticosteroids is allowed).

b) Receipt of parenteral steroids (equivalent to 20 mg/day prednisone ≥12 weeks/≥2 mg/kg body weight/day prednisone ≥2 weeks) within 60 days prior to Day 1 (M0).

c) Administration of immunoglobulins and/or any blood products within the 3 months prior to Day 1 (M0) or planned administration during the trial.

d) Receipt of immunostimulants within 60 days prior to Day 1 (M0).

e) Immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy within 6 months prior to Day 1 (M0).

f) Human immunodeficiency virus (HIV) infection or HIV-related disease.

g) Hepatitis B virus infection.

h) Hepatitis C virus infection.

i) Genetic immunodeficiency.

8. Abnormalities of splenic or thymic function.
9. Subjects with a known bleeding diathesis, or any condition that may be associated with a prolonged bleeding time.
10. Subjects with any serious chronic or progressive disease according to the judgment of the investigator (eg, neoplasm, hematologic malignancies, insulin dependent diabetes, cardiac, renal or hepatic disease).
11. Subjects participating in any clinical trial with another trial vaccine 30 days prior to Day 1 (M0) or intending to participate in another clinical trial at any time during the conduct of this trial.
12. Subjects who received any other vaccines within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to enrollment in this trial or who are planning to receive any vaccine within 28 days of trial vaccine administration.
13. Subjects who have used antipyretics and/or analgesic medications within 24 hours prior to vaccination. The reason for their use (prophylaxis versus treatment) must be documented. Trial entry should be delayed to allow for a full 24 hours to have passed since last use of antipyretics and/or analgesic medications.
14. Subjects involved in the trial conduct or their first-degree relatives.
15. Subjects with a history of substance or alcohol abuse within the past 2 years.
16. Subjects who are pregnant or breastfeeding.
17. Females of childbearing potential who are sexually active and who have not used any of the acceptable contraceptive methods for at least 2 months prior to Day 1 (M0).

    a) Of "childbearing potential" is defined as status post-onset of menarche and not meeting any of the following conditions: menopausal for at least 2 years, status after bilateral tubal ligation for at least 1 year, status after bilateral oophorectomy, or status after hysterectomy.

b) "Acceptable birth control methods" are defined as one or more of the following:

I. Hormonal contraceptive (such as oral, injection, transdermal patch, implant, cervical ring).

II. Intrauterine device.

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

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

18. Females of childbearing potential who are sexually active and who refuse to use an acceptable contraceptive method up to 6 weeks post-final vaccination on Day 180 (M6). In addition, they must be advised not to donate ova during this period (see Section 9.1.9).
19. Any positive or indeterminate pregnancy test (see Section 9.1.10).
20. Previous and planned vaccination (during the trial conduct), against any flavivirus (except Japanese encephalitis [JE]) including dengue, yellow fever (YF) viruses or tick-borne encephalitis.
21. Previous and planned vaccination (during the trial conduct) against HPV.
22. Previous participation in any clinical trial of a dengue or other flavivirus (eg, West Nile [WN] virus) candidate vaccine, except for subjects who received placebo in those trials.
23. Subjects with a current or previous infection with a flavivirus such as Zika, YF, JE, WN fever, tick-borne encephalitis or Murray Valley encephalitis.

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

7.3 Criteria for Delay of Trial Vaccine Administration at Day 90 (M3) and Day 180 (M6) in Group 1, and Day 180 (M6) in Group 2

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

If any of the criteria below occur at the time scheduled for the trial vaccine administration at Day 90 (M3) and Day 180 (M6) in Group 1, and Day 180 (M6) in Group 2, the subsequent dose may be administered at a later date as long as the subject is otherwise eligible to continue trial participation. In certain situations, the period of delay may lead to deviation from the time window for the subsequent dose. The decision to vaccinate in those situations will be made by the investigator.

The following clinical circumstances warrant a delay in the administration of trial vaccine at Day 90 (M3) and Day 180 (M6) in Group 1, and Day 180 (M6) in Group 2:

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

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

Under some circumstances, a subject's trial participation may be terminated early. This means that no further trial procedures (including data collection) will be performed on that subject beyond the specific date of early termination of trial participation. The primary reason for early termination of the subject's trial participation should be documented using the following categories. While the subject has no obligation to provide a reason for withdrawing consent, attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be documented.

For screen failure subjects, refer to Section 9.1.11.

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

If the clinical trial is prematurely terminated by the sponsor, the investigator is to promptly inform the trial subjects and local IEC/IRB and should assure appropriate follow up for the subjects. The primary reason for early termination in this case will be "trial termination".

5. Subject's death during trial participation.
6. Other (the specific reason should be recorded in the "Specify" field of the eCRF).

7.5 Criteria for Premature Discontinuation of Trial Vaccine Administration

There are also circumstances under which receipt of the trial vaccination is contraindicated in this trial (Day 90 [M3] and Day 180 [M6] in Group 1, or Day 180 [M6] in Group 2 only).

These circumstances include but are not limited to anaphylaxis or severe hypersensitivity reactions following the administration of an earlier trial vaccination at Day 1 (M0) and Day 90 (M3) in Group 1, or Day 1 (M0) in Group 2. If these reactions occur, the subject must not receive the trial vaccination at Day 90 (M3) and Day 180 (M6) in Group 1, or Day 180 (M6) in Group 2, respectively, but the subject will be encouraged to continue trial participation for safety follow-up.

Early termination of a subject's trial participation will by default prevent the subject from receiving further doses of trial vaccine, as the subject will no longer be participating in the trial.

In addition to criteria for early termination of a subject's participation (see Section 7.4), other situations may apply in which subjects may continue participating in the trial (eg, contributing safety data according to the protocol) but trial vaccine administration is discontinued. Even if the subject is deemed ineligible to receive further doses of trial vaccine, all efforts should be made to continue the collection of safety data according to the protocol.

In addition, the primary reason for premature discontinuation of trial vaccine administration should be recorded in the eCRF "End of Trial Vaccine administration" page using the following categories:

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

If the clinical trial is prematurely terminated by the sponsor, the investigator is to promptly inform the trial subjects and local IEC/IRB and should assure appropriate follow-up for the subjects. The primary reason for early termination in this case will be 'trial termination".

5. Subject's death during trial participation.
6. Protocol deviation: a protocol deviation is any change, divergence, or departure from the trial design or procedures of a trial protocol. The subject may remain in the trial unless continuation in the trial jeopardizes the subject's health, safety or rights (see Section 7.4).
7. Pregnancy: any subject who, despite the requirement for adequate contraception, becomes pregnant during the trial will not receive further trial vaccine administration(s). Pregnant subjects should, however, be asked to continue participating in the trial contributing data to the safety follow-up according to protocol. In addition, the site should maintain contact with the pregnant subject and complete a "Pregnancy Form" as soon as possible. The subject should be followed-up until the birth of the child, or spontaneous or voluntary termination; when pregnancy outcome information becomes available, the information should be captured using the same form. Data obtained from the "Pregnancy Form" will be captured in the safety database.
8. Other (the specific reason should be recorded in the "Specify" field of the eCRF).

8.0 CLINICAL TRIAL MATERIAL MANAGEMENT

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

8.1 Trial Vaccines and Materials

Investigational vaccine

TDV kits (TDV and TDV diluent)

The investigational vaccine, TDV, is a Dengue Tetravalent Vaccine (Live, Attenuated) comprised of a molecularly characterized, attenuated dengue serotype 2 strain (TDV-2), a dengue serotypes 2/1 recombinant strain (TDV-1), a dengue serotypes 2/3 recombinant strain (TDV-3), and a dengue serotypes 2/4 recombinant strain (TDV-4) with potencies of not less than 3.3, 2.7, 4.0 and 4.5 $\log_{10}$ plaque forming units per dose of TDV-1, TDV-2, TDV-3, and TDV-4, respectively. TDV is a lyophilized vaccine that will be reconstituted in diluent (37 mM NaCl solution) prior to administration. Refer to the IB for a detailed description.

Concomitant vaccine

9vHPV vaccine

The 9vHPV vaccine (Merck) is a recombinant 9-valent vaccine containing the L1 proteins for HPV types 6, 11, 16, 18, 31, 33, 45, 52, and 58. The 9vHPV vaccine contains yeast protein, and the vaccine antigen is adsorbed on an aluminum-containing adjuvant. Each dose of 9vHPV vaccine is 0.5 mL and is supplied as a single-dose vial or in prefilled syringes that do not contain latex. Refer to the prescribing information of 9vHPV vaccine for a detailed description.

Details regarding the dosage form description and strengths, or composition for the extemporaneous preparation of the trial vaccine can be found in the pharmacy manual or in the referenced compounding manual when applicable. Trial vaccine will be packaged to support enrollment.

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

TDV kits (TDV and TDV diluent)

Manufacturing of monovalent bulk vaccine substances of TDV, mixing of the 4 TDV vaccine substances, filling into vials, and lyophilization of TDV is done at IDT Biologika GmbH, Germany.

Lyophilized TDV is presented in a single-dose 2 mL glass vial with a grey butyl rubber stopper and flip-top aluminum overseal.

TDV diluent (37 mM sodium chloride solution) is a clear, colorless solution provided in a single-use 2 mL glass vial or a single-use 1 mL glass syringe and is used to reconstitute the lyophilized TDV to deliver a 0.5 mL dose.

The sponsor will supply TDV and TDV diluent vials/syringes packaged together into single dose dispensing cartons. The units and cartons will be labeled with pertinent trial information in local languages. Further details can be found in the Pharmacy Manual.

9vHPV vaccine

The 9vHPV vaccine is manufactured by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.

The 9vHPV vaccine is presented in a 0.5 mL suspension for injection as a single-dose vial or as a prefilled syringe. The vaccine is prepared from the purified virus-like particles of the major capsid (L1) protein of HPV Types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

The purified virus-like particles are adsorbed on preformed aluminum-containing adjuvant: amorphous aluminum hydroxyphosphate sulfate.

The vaccine is a sterile liquid suspension that is prepared by combining the adsorbed virus-like particles of each HPV type and additional amounts of the aluminum-containing adjuvant and the final purification buffer.

Each 0.5 mL dose contains approximately 30 µg of HPV Type 6 L1 protein, 40 µg of HPV Type 11 L1 protein, 60 µg of HPV Type 16 L1 protein, 40 µg of HPV Type 18 L1 protein, 20 µg of HPV Type 31 L1 protein, 20 µg of HPV Type 33 L1 protein, 20 µg of HPV Type 45 L1 protein, 20 µg of HPV Type 52 L1 protein, and 20 µg of HPV Type 58 L1 protein.

Each 0.5 mL dose of the vaccine also contains approximately 500 µg of aluminum (provided as amorphous aluminum hydroxyphosphate sulfate), 9.56 mg of sodium chloride, 0.78 mg of L-histidine, 50 µg of polysorbate 80, 35 µg of sodium borate, <7 µg yeast protein, and water for injection. The product does not contain a preservative or antibiotics.

After thorough agitation, 9vHPV vaccine is a white, cloudy liquid.

The sponsor will supply the trial site with the 9vHPV vaccine. The units and cartons will be labeled with pertinent trial information in local languages. Further details can be found in the Pharmacy Manual.

8.1.2 Storage

Investigational vaccine

TDV and TDV diluent will be shipped in refrigerated containers at 2°C to 8°C. From receipt and prior to use, TDV and TDV diluent must be protected from light and stored at 2°C to 8°C in a refrigerator, but must not be frozen.

Concomitant vaccine

9vHPV vaccine will be shipped in refrigerated containers at 2°C to 8°C. From receipt and prior to use, 9vHPV vaccine must be protected from light and stored at 2°C to 8°C in a refrigerator, but must not be frozen.

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

8.1.3 Dose and Regimen

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

The 0.5 mL trial vaccine doses of TDV and 9vPHV will be prepared and administered by the pharmacist or vaccine administrator according to the instructions in the Pharmacy Manual or per sponsor instructions.

TDV will be administered by the SC route, and 9vHPV vaccine will be administered by the intramuscular (IM) route.

Table 8.a Sponsor-Supplied Trial Vaccines

Group	Number of subjects	Day 1 (M0)	Day 90 (M3)	Day 180 (M6)
Group 1	307	TDV+9vHPV	TDV	9vHPV
Group 2	307	9vHPV		9vHPV

Note: co-administered trial vaccines will be injected in opposite arms.
9vHPV=Recombinant 9-valent human papillomavirus vaccine, M=month, TDV=Dengue Tetravalent Vaccine (Live, Attenuated).

8.2 Trial Vaccine Assignment and Dispensing Procedures

Trial vaccines will be identifiable by a unique identification number and managed by Interactive Response Technology (IRT). Refer to Section 8.6 for accountability of sponsor-supplied vaccines.

The investigator or designee will use IRT at subject enrollment to obtain the subject number (see Section 9.1.1). This number will be used throughout the trial.

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

The investigator or designee will be responsible for overseeing the administration of vaccine(s) to subjects enrolled in the trial according to the procedures stipulated in this trial protocol. The vaccine will be administered only by personnel who are qualified to perform that function under applicable laws and regulations for that specific trial.

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

8.2.1 Precautions to be Observed When Administering the Trial Vaccine(s)

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

First, trial eligibility is evaluated according to the entry criteria outlined in this protocol (Sections 7.1 and 7.2). Once eligibility is confirmed, the subject will receive the first trial vaccination(s) (Day 1 [M0]) according to random trial group allocation.

Prior to subsequent trial vaccine administration (on Day 90 [M3] for Group 1, and on Day 180 [M6] for Group 1 and 2), site staff must determine if the subject is eligible to receive vaccination by evaluating the criteria outlined in Sections 7.3, 7.4 and 7.5.

Trial vaccine(s) should not be administered to individuals with known hypersensitivity to any component of the vaccine(s).

Standard immunization practices are to be observed and care should be taken to administer the injection by the SC (TDV) or IM (9vHPV) route. In addition, WHO recommendations to reduce anxiety and pain at the time of vaccination should be followed [23]. Before administering the trial vaccine(s), the vaccination site(s) must be disinfected with a skin disinfectant (eg, 70% alcohol). Allow the skin to dry. In Group 1 on Day 1 (M0), concomitant vaccine administration (TDV and 9vHPV) vaccine will be injected in opposite arms. Refer to the pharmacy manual for details on preparation and administration of trial vaccination.

After each trial vaccination (TDV and/or 9vHPVvaccine), the subject will be observed for at least 30 minutes for severe reactions. As with all injectable vaccines, trained medical personnel and appropriate medical treatment should be readily available in case of anaphylactic reactions following vaccination. For example, epinephrine 1:1000, diphenhydramine, and/or other medications for treating anaphylaxis should be available. These rescue medications will not be supplied by the sponsor.

8.3 Randomization Code Creation and Storage

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.

8.4 Trial Vaccine Blind Maintenance

To prevent bias or the perception of bias, study team members responsible for decision making regarding study conduct or analysis of data after the first subject enrollment (eg protocol amendment and SAP amendment) will be documented in the data access management plan, and will be independent of unblinded data review.

8.5 Unblinding Procedure

Not applicable.

8.6 Accountability and Destruction of Sponsor-Supplied Trial Vaccine

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

The investigator or designee must ensure that the sponsor-supplied trial vaccine(s) (TDV including TDV diluent, 9vHPV vaccine) are used in accordance with the approved protocol and is/are administered only to subjects enrolled in the trial. To document appropriate use of sponsor-supplied trial vaccine(s) (TDV including TDV diluent, 9vHPV vaccine), the investigator must maintain records of all sponsor-supplied trial vaccine(s) delivery to the site, site inventory, administration and use by each subject, and destruction or return to the sponsor or designee.

Upon receipt of sponsor-supplied trial vaccine(s), the investigator or designee must verify the contents of the shipments against the packing list. The verifier should ensure that the quantity is correct, the trial vaccines are received within the labeled storage conditions (ie, no cold chain break has occurred during transit), and are in good condition. If quantity and conditions are acceptable, investigator or designee will acknowledge receipt of the shipment by recording in IRT.

If there are any discrepancies between the packing list versus the actual product received, the sponsor or designee must be contacted to resolve the issue. The packing list should be filed in the Pharmacy Investigator Site File by a qualified investigator designee.

The investigator (or designated individual) must maintain 100% accountability for all sponsor-supplied trial vaccines (TDV including TDV diluent, 9vHPV vaccine) received and administered during their entire participation in the trial. Accountability includes, but is not limited to:

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

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

The pharmacist (or designated individual) at the site must record the current inventory of all sponsor-supplied vaccines (TDV including TDV diluent, 9vHPV vaccine) on a sponsor-approved trial vaccine accountability log. The following information will be recorded as a minimum: protocol number and title, name of investigator, site identifier and number, description of sponsor-supplied trial vaccines, expiry and/or retest date, and amount. The log should include all required information as a separate entry for each subject to whom sponsor-supplied trial vaccine(s) is administered.

The investigator will be notified of any expiry date or retest date extension of trial vaccine(s) or clinical trial material during the trial conduct. On expiry date notification from the sponsor, the site

must complete all instructions outlined in the notification, including segregation of expired clinical trial material for return to the sponsor or its designee for destruction.

Prior to site closure or at appropriate intervals throughout the trial, before any trial vaccine(s) are destroyed locally or clinical trial materials are returned to the sponsor or 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.

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

The Schedule of Trial Procedures is located in Section 2.1.

9.1.1 Informed Consent and Pediatric Assent Form

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

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

A unique subject number will be assigned to each subject by the IRT after informed consent or pediatric assent is obtained. If all eligibility criteria are fulfilled, this subject number will be used throughout the trial. Subject numbers assigned to subjects who fail screening assessments on Day 1 (M0) should not be reused (see Section 9.1.11).

9.1.2 Demographics, Medical History and Prior Medications

Demographic information to be obtained on Day 1 (M0) will include age/date of birth, sex, race, and ethnicity as described by the subject or subject's LAR.

Medical history will be collected (Day 1 [M0]), including but not limited to any medical history that may be relevant to subject eligibility for trial participation such as prior medications/vaccinations and previous and ongoing illnesses and/or injuries. Use of concomitant medications/vaccinations will be collected throughout the trial until Day 360 (M12). Relevant medical history can also include any medical history that contributes to the understanding of an AE that occurs during trial participation, if it represents an exacerbation of an underlying disease/preexisting problem.

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

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

All medications, vaccines and blood products taken or received by the subjects are to be collected as "Prior and Concomitant Medications" and recorded on the "Prior and Concomitant Medications" eCRF and in the subject's source document:

- Medications: from 1 month (minimum 28 days) prior to administration of each trial vaccine dose up to 1 month (minimum 28 days) thereafter.
- Vaccines: from 1 month (minimum 28 days) prior to administration of each trial vaccine dose up to 1 month (minimum 28 days) thereafter.
- Steroids and immunostimulants within 60 days prior to Day 1 (M0).
- Immunoglobulins and blood products within 3 months prior to Day 1 (M0).
- Immunosuppressive therapy within 6 months prior to Day 1 (M0).

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 medications within 24 hours prior to vaccine administration (see Section 7.3).

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

Prohibited therapies (see also Section 7.2):

- Parenteral immunoglobulin preparation, blood products, and/or blood-derived products within 3 months prior to Day 1 (M0).
- Immunosuppressive therapy within 6 months or systemic (eg, oral or parenteral) corticosteroid treatment within 60 days prior to Day 1 (M0) or immunostimulants within 60 days prior to Day 1 (M0).
- Any other vaccines within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to Day 1 (M0) and Day 90 (M3), and 28 days after each trial vaccination.
- Use of antipyretics and/or analgesic medications within 24 hours prior to trial vaccine administration at Day 1 (M0), or Day 90 (M3) and Day 180 (M6). Trial vaccine administration should be delayed to allow for a full 24 hours to have passed since last use of antipyretics and/or analgesic medications.
- Any other dengue vaccines (investigational or licensed) for the entire trial period.
- Receipt of any other clinical trial product within 30 days prior to Day 1 (M0).

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

9.1.3 Documentation of Trial Entrance/Randomization

Only subjects who have a signed a pediatric assent form and informed consent form, meet all of the inclusion criteria and none of the exclusion criteria are eligible for randomization into this trial.

The randomization schedule will be created and controlled by the IRT provider. The randomization specification will be approved by the sponsor's trial statistician, or designee.

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

9.1.4 Physical Examination

Physical examinations must be performed by a qualified health professional in accordance with local regulations and as listed within the Site Responsibility Delegation Log.

A complete physical examination will be performed on Day 1 (M0), Day 90 (M3) and Day 180 (M6) according to the investigator's standard practice. A complete physical examination includes but is not limited to: auscultation of heart and lungs, palpation of the abdomen, inspection of extremities (including skin over intended vaccination site[s]), a check of general appearance and the measurement of weight and height; body mass index will be calculated automatically.

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 will be performed on Day 30 (M1), Day 120 (M4), Day 210 (M7), and Day 360 (M12) and includes but not limited to the measurement of vital signs (see Section 9.1.5). Significant clinical differences from the baseline assessment must be recorded in the subject's source documents and the "adverse event" eCRF.

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

9.1.5 Vital Signs

Vital signs will be recorded on Day 1 (M0), Day 30 (M1), Day 90 (M3), Day 120 (M4), Day 180 (M6), Day 210 (M7), and Day 360 (M12). These will include (but are not limited to) the measurement of systolic blood pressure/diastolic blood pressure, heart rate, and body temperature.

9.1.6 Immunogenicity Assessments

Blood samples for the measurement of HPV neutralizing antibodies (Merck assay) for both Groups 1 and 2 will be collected at pre-first vaccination (Day 1 [M0]) and at 1 month (at least 29 days) post-second 9vHPV vaccination (Day 210 [M7]).

Blood samples for the measurement of dengue neutralizing antibodies (by MNT_{50}) will be collected for Group 1 only at pre-first vaccination (Day 1 [M0]) and at 1 month (at least 29 days) post-second TDV vaccination (Day 120 [M4]).

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

9.1.7 Processing, Labeling and Storage of Biological Samples

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

9.1.8 Safety Assessments

Safety assessments will include collection and recording of solicited local (injection site) reactions and solicited systemic AEs, unsolicited AEs (serious and non-serious), and pregnancies.

Refer to Section 10.1 for safety definitions. Details on collection and reporting of AEs are in Section 10.4.

9.1.9 Contraception and Pregnancy Avoidance Procedure

For female subjects of child bearing potential, urine pregnancy testing will be performed prior to each trial dose administration (for both Groups 1 and 2 on Day 1 [M0] and Day 180 [M6], and for Group 1 only on Day 90 [M3]).

Female subjects will be provided with information on acceptable methods of contraception as part of the subject informed consent process and will be asked to sign a consent form stating that they understand the requirements for avoidance of pregnancy and donation of ova. Subjects will receive continued guidance with respect to the avoidance of pregnancy as part of the trial procedures, and females of childbearing potential who are sexually active will be reminded during trial visits to adhere to acceptable contraceptive methods (as defined in exclusion criterion number 17b) up to 6 weeks after the last dose of TDV (Day 90 [M3] + 6 weeks) or 6 weeks after the last dose of 9vHPV (Day 180 [M6] + 6 weeks). The investigator or designee should explain pertinent aspects of the trial in an age appropriate manner to pediatric subjects in accordance with local regulations.

Refer also to Sections 2.1 and 7.2.

9.1.10 Pregnancy

To ensure female subject safety and the safety of the unborn child, each pregnancy in a subject having received a trial vaccine must be reported to the sponsor within 24 hours of the site learning of its occurrence. If a subject becomes pregnant during the trial, she will not receive any further doses of any trial vaccine. The pregnancy must be followed to determine outcome, including spontaneous or voluntary termination, details of birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications. This follow-up should occur even if the intended duration of safety follow-up for the trial has ended.

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

9.1.11 Documentation of Subjects Who Are Not Randomized

Investigators must account for all subjects who sign an informed consent or who have a signed pediatric assent form. If the subject is found to be not eligible at this visit (Day 1 [M0]), the investigator should complete the eCRF accordingly.

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

- Adverse medical occurrence prior to receipt of investigational vaccine(s).
- Screen failure (did not meet one or more inclusion criteria or did meet one or more exclusion criteria)
- Withdrawal by subject
- Trial terminated by the sponsor
- Site terminated by sponsor.
- Other (specify reason)

Subject numbers assigned to subjects who fail eligibility procedures on Day 1 (M0) should not be re-used.

9.2 Monitoring Subject Compliance

The investigator or designee records all administrated injections of trial vaccines (TDV, 9vHPV vaccine) given to the subject in the subject's source document and the eCRF.

9.3 Schedule of Observations and Procedures

The schedule for all trial-related procedures for all evaluations is shown in Table 2.a in Section 2.1. Assessments should be completed at the designated visit(s)/time point(s). Visit windows will be counted from the day of vaccination (Day 1, Day 90 and Day 180 for Group 1; Day 1 and Day 180 for Group 2) with *at least* 29 days before the next scheduled clinic visit.

9.3.1 Pre-Vaccination Procedures (Day 1 [M0], Day 90 [M3] and Day 180 [M6])

Pre-vaccination procedures will be performed for all subjects (Group 1 and 2) on Day 1 (M0). Unless otherwise stated these procedures will be repeated on Day 90 (M3) for Group 1 only, and on Day 180 (M6) for Group 1 and 2.

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

4. Collect concomitant medications/vaccinations data. Refer to Section 9.1.2.
5. Review of systems: review of systems is a structured interview that queries the subject as to any complaints the subject has experienced across each organ system.
6. Perform a complete physical examination (Day 1 [M0]). Refer to Section 9.1.4.
7. Check vital signs (Day 1 [M0]). Refer to Section 9.1.5.
8. Perform pregnancy testing (urine) for females of childbearing potential on Day 1 [M0], Day 90 [M3] and Day 180 [M6] in Group 1, and on Day 1 [M0], Day 180 [M6] in Group 2. Refer to Section 9.1.10.
9. Provide guidance with respect to the avoidance of pregnancy for females of childbearing potential who are sexually active with men. Refer to Section 9.1.9.
10. Randomize the subject (Day 1 [M0]).
11. Collect a blood sample prior to vaccination on Day 1 (M0) from subjects in Group 1 and 2. Refer to Sections 9.1.6.

Blood should be taken from the subject using an aseptic venipuncture technique for serological immunogenicity testing.

9.3.2 Vaccination Procedures (Day 1 [M0], Day 90 [M3] and Day 180 [M6])

Vaccination procedures will be performed for all subjects (Group 1 and 2) on Day 1 (M0), unless otherwise stated these procedures will be repeated on Day 90 (M3) for Group 1 only, and on Day 180 (M6) for Group 1 and 2.

1. Check criteria for delay of trial vaccination (for Group 1 on Day 90 [M3] and Day 180 [M6], and for Group 2 only on Day 180 [M6]). Refer to Section 7.3.
2. Check contraindications to trial vaccination (for Group 1 on Day 1 [M0], Day 90 [M3] and Day 180 [M6], and for Group 2 on Day 1 [M0] and Day 180 [M6]). Refer to Section 7.5.
3. Vaccinate the subject. Refer to Section 8.1.3 and 8.2.

9.3.3 Post-Vaccination Procedures (Day 1 [M0], Day 90 [M3] and Day 180 [M6])

Post-vaccination procedures will be performed for all subjects (Group 1 and 2) on Day 1 (M0), unless otherwise stated these procedures will be repeated on Day 90 (M3) for Group 1 only, and on Day 180 (M6) for Groups 1 and 2.

- Perform post-vaccination observation (refer to Section 8.2.1).
- Careful training of the subject or the subject's LAR on how to measure solicited local (injection site) reactions and body temperature, how to complete the diary card and how often to complete the diary card. Training should be directed at the individual(s) who will perform the measurements of solicited local (injection site) reactions and those who will enter the information into the diary card. This individual may or may not be the subject or the subject's

LAR, but if a person other than the subject or the subject's LAR enters information into the diary card, this person's identity must be documented in the source and this person must receive training on the diary card. Training of the subject or the subject's LAR on how to measure an injection site reaction and how to take their temperature, as well as how to record the information in the diary card, should be performed while the subject is under observation after vaccination. Training of the subject or subject's LAR should be documented in the subject's source document.

Diary card instructions must include the following:

- The individual(s) who will enter the information into the diary card must understand that timely completion of the diary card on a daily basis is a critical component of trial participation. This individual should also be instructed to write clearly and to complete the diary card in pen. Any corrections to the diary card that are performed by the individual(s) completing the diary card should include a single strikethrough line with a brief explanation for any change and be initialed and dated.

Please note:

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

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

change in the subject's health status, and any medications taken (excluding vitamins and minerals). These solicited AEs (solicited local [injection site] reactions or solicited systemic AEs) and body temperature will be recorded in the diary. Assessments should preferably take place in the evening at day's end.

- Body temperature measurement is to be performed using the thermometer provided by the site. If the subject feels unusually hot or cold during the day, the subject should check their temperature. If the subject has fever, the highest body temperature observed that day should be recorded in the diary card.
- The measurements of solicited local (injection site) reactions (pain, erythema, and swelling) are to be performed using the ruler provided by the site.
- The diary cards will be reviewed and collected on Day 30 (M1) (Groups 1 and 2) and on Day 120 (M4) (Group 1).
- In the diary card, the collection of solicited local (injection site) reactions, and solicited systemic AEs (including body temperature measurement) and unsolicited AEs (non-serious) will continue for a total of 7 days, 14 days, and 28 days, respectively, following administration of trial vaccine dose (including the day of administration) on Day 1 (M0) in Groups 1 and 2, and on Day 90 (M3) in Group 1 only. Any solicited local (injection site) reaction or solicited systemic AEs observed as continuing on Day 8 or Day 15, respectively, following trial vaccination on Day 1 (M0) in Groups 1 and 2, and on Day 90 (M3) in Group 1 only will be recorded as an AE on the "Adverse Event" eCRF for follow-up. Any solicited local (injection site) reaction(s) or systemic AE that resolves before 8 or 15 days, respectively, following each trial vaccination, but recurs at a later time (ie, if discontinued), should be recorded as an unsolicited AE on the "Adverse Event" eCRF (see Sections 10.4.1 and 10.4.2).
- Provide guidance with respect to the avoidance of pregnancy for females of childbearing potential who are sexually active with men. Refer to Section 9.1.9.
- Collect and report SAEs. Refer to Section 10.4.4.

After each trial vaccination, the subject will be observed for at least 30 minutes including observation for solicited local (injection site) reactions, solicited systemic AEs (including body temperature measurement), and unsolicited AEs. Information should be recorded in the eCRF. The investigator or delegate will take the opportunity to remind the subject and/or the subject's LAR how to measure solicited local (injection site) reactions and body temperature as part of this observation period. All safety data will be collected in the subject's source documents.

The investigator or delegate should schedule the next site visit or other trial activity with the subject or the subject's LAR.

The subject or subject's LAR will receive a written reminder of the next scheduled trial visit.

The subject or the subject's LAR will be reminded to complete the diary card daily and to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is

medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit. All contact details will be provided to the subject or subject's LAR.

9.3.4 Site Visits after Vaccination (Day 30 [M1], Day 120 [M4] and Day 210 [M7])

Clinic visits that do not include a vaccination will be performed on Day 30 (M1), Day 120 (M4) and Day 210 (M7). These visits should occur at least 29 days after the first TDV and 9vHPV vaccinations on Day 1 (M0), the second TDV vaccination (Group 1 only) on Day 90 (M3) and the second 9vHPV vaccination on Day 180 (M6) (see also Section 9.3).

1. Interview the subject or subject's LAR and check the diary card (for Group 1: Day 30 [M1] and Day 120 [M4]; and for Group 2: Day 30 [M1]). Refer to Section 9.3.3.
2. Collect information of concomitant medication(s)/vaccination(s). Refer to Section 9.1.2.
3. Perform a targeted physical examination. Refer to Section 9.1.4.
4. Check vital signs. Refer to Section 9.1.5.
5. Provide guidance with respect to the avoidance of pregnancy for females of childbearing potential who are sexually active with men. Refer to Section 9.1.9.
6. Collect and record persistent/prolonged solicited local (injection site) reactions. Refer to Sections 9.3.3 and 10.4.2.
7. Collect and record persistent/prolonged solicited systemic AEs. Refer to Sections 9.3.3 and 10.4.2.
8. Collect and record SAEs. Refer to Section 10.4.4.
9. Collect a blood sample from the subject (Day 120 [M4] in Group 1, and Day 210 [M7] in Groups 1 and 2). Refer to Section 9.1.6.

   Blood should be taken from the subject using an aseptic venipuncture technique for serological immunogenicity testing.

The investigator or delegate should schedule the next site visit or other trial activity with the subject or the subject's LAR.

The subject or subject's LAR will receive a written reminder of the next scheduled trial visit, as applicable.

The subject or the subject's LAR will be reminded to contact the site if there are any questions and to contact the site immediately (or as soon as the subject is medically stable) if the subject has a medical condition that leads to a hospitalization or an emergency room visit. All contact details will be provided to the subject or subject's LAR.

9.3.5 Phone Contacts - Reminder Calls

Not applicable.

9.3.6 Phone Contacts – Safety Call

When a site visit cannot be carried out due to the COVID-19 pandemic, alternative methods of contact (e.g telephone contact) will be made for subjects who are still under monitoring for safety reporting.

9.3.7 Final (End of Trial) Visit (Day 360 [M12])

The final (end of trial) visit will be performed on Day 360 (M12). If a subject terminates earlier, the final visit procedures should be performed at their last trial visit, if possible. For all subjects receiving trial vaccine(s), the investigator must complete the "End of Trial" eCRF page.

Review of systems (Day 360 [M12]: review of systems is a structured interview that queries the subject or the subject's LAR as to any complaints the subject has experienced across each organ system.

9.3.8 Post-Trial Care

No post-trial care will be provided.

9.4 Biological Sample Retention and Destruction

In this trial, specimens for immune response testing will be collected as described in Section 9.1.6. All blood samples will be processed, labeled and stored according to the Laboratory Manual or other appropriate guideline provided to the site. 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 subject's personal information to ensure optimal confidentiality and defined standard processes for sample and data collection, storage, analysis, and destruction.

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

10.0 ADVERSE EVENTS

10.1 Definitions

10.1.1 Adverse Events

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

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

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

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

10.1.2 Solicited Adverse Events

The occurrence of selected indicators of safety will be measured/collected for 7 days (solicited local [injection site] reactions) and 14 days (solicited systemic AEs) following administration of each trial vaccine dose (including the day of administration) and will be recorded on the "Local and Systemic Reactions" eCRF page as applicable and as listed in Table 10.a.

Any solicited local (injection site) reactions or solicited systemic AEs observed as continuing on Day 8 or Day 15, respectively, following each trial vaccination will be recorded as an AE on the "Adverse Event" eCRF for follow-up. For these persistent/prolonged solicited AEs the end date will be captured on the "Adverse Event" eCRF to permit a separate analysis from the unsolicited AEs (see Sections 10.4.1 and 10.4.2).

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

Local (injection site) reactions	Pain Erythema Swelling
Systemic events (adult/adolescent/child ≥6 years)	Fever [(a)] Headache Asthenia Malaise Myalgia

(a) Fever is defined as body temperature greater than or equal to 38°C (100.4°F) regardless of method taken [20].

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

Table 10.b Severity Scales for Solicited Parameters

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

(a) Subjects or the subject's legally authorized representatives are to record greatest surface diameter in mm on the diary card.
(b) Fever is defined as body temperature greater than or equal to 38°C (100.4°F) regardless of method taken [20].

10.1.3 Adverse Events of Special Interest

Not applicable.

10.1.4 Medically-Attended Adverse Events

Not applicable.

10.1.5 Serious Adverse Events

An SAE is defined as any untoward medical occurrence that:

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

10.2 Causality of AEs

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

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

10.2.1 Relationship to Trial Procedures

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

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

10.2.2 Outcome of Adverse Events

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

10.3 Additional Points to Consider for Adverse Events

An untoward occurrence generally may:

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

Diagnoses versus signs and symptoms:

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

Worsening of AEs:

- If the subject experiences a worsening or complication of an AE after administration of the trial vaccine, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").
- If the subject experiences a worsening or complication of an AE, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (eg, "worsening of…").

Changes in severity of AEs:

- If the subject experiences changes in severity of an AE, the event should be captured once with the maximum severity recorded.

Preplanned surgeries or procedures:

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent/pediatric assent form are not considered AEs. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

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

Trial procedures:

- Adverse occurrences related to trial procedures after signing of informed consent/pediatric assent form are considered as AEs and should be reported as AEs.

10.4 Procedures

10.4.1 Collection and Reporting of Adverse Events

All AEs, whether considered related to the use of the trial vaccine(s) or not, must be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full autopsy report should be supplied, if possible. All findings must be reported on an AE eCRF and on the SAE form[(a)], if necessary (see Section 10.4.4). All findings in subjects experiencing AEs must also be documented in the subject's source documents. Any unsolicited AEs will be collected for 28 days (day of vaccination + 27 subsequent days) following each trial vaccination during site visits via interview. AEs leading to discontinuation (from the trial or from the vaccination regimen) are collected throughout the trial. Even if the subject is deemed ineligible to receive further doses of trial vaccine, all efforts should be made to continue the collection of safety data according to protocol.

The following information will be documented for each event:

- Reported term for the AE.
- Start and end date.
- Serious (Y/N).
- Severity.
- Investigator's opinion of the causality (relationship) between the event and administration of trial vaccine(s) ("related" or "not related").

- Investigator's opinion of the causality (relationship) to trial procedure(s), including the details of the suspected procedure.
- Action taken with the trial vaccine(s).
- Outcome of event.

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

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 or subjects' LAR for 7 days (solicited local [injection site] reactions) and 14 days (solicited systemic AEs) following administration of each trial vaccine dose (including the day of administration) and will be recorded on the "Local and Systemic Reactions" eCRF, as applicable. These will be summarized in the final report under the category "solicited AEs" to differentiate them from unsolicited AEs.

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

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

- Solicited local (injection site) reactions or systemic AEs that lead the subject to withdraw from the trial.
- Solicited local (injection site) reactions or systemic AEs that lead to the subject being withdrawn from the trial by the investigator.
- Solicited local (injection site) reactions or systemic AEs that otherwise meet the definition of an SAE (see Section 10.1.2 and 10.1.5).

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

Adverse Events of Special Interest and/or Medically-Attended Adverse Events will not be collected.

10.4.4 Collection and Reporting of Serious Adverse Events

Collection of SAEs will commence from the time that the subject is 'first' administered the trial vaccine (Day 1 [M0]). Routine collection of SAEs will continue until the end of the trial (Day 360 [M12]).

SAEs should be reported according to the following procedure:

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

- A short description of the event and the reason why the event is categorized as serious.
- Causality assessment.
- Protocol number.
- Subject identification number.
- Investigator's name.
- Name of trial vaccine(s).

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

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

10.5 Follow-up Procedures

10.5.1 Adverse Events

All AEs will be monitored until resolution or a stable status is reached or until a formal diagnosis can be made or until the end of the trial, whichever occurs first.

10.5.2 Serious Adverse Events

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

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

10.5.3 Safety Reporting to Investigators, Investigational Review Boards or Independent Ethics Committees, and Regulatory Authorities

The sponsor or designee will be responsible for the reporting of all Suspected Unexpected Serious Adverse Reactions (SUSAR) and any other SAEs to regulatory authorities, investigators and IRBs or IECs, as applicable, in accordance with national regulations in the countries where the trial is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or designee, SUSARs will be submitted within 7 days for fatal and life-threatening events and 15 days for other SUSARs, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the

current benefit-risk assessment of an investigational vaccine or that would be sufficient to consider changes in the trial vaccine administration or in the overall conduct of the trial. The investigational site also will also forward a copy of all expedited reports to their IRB or IEC in accordance with national regulations.

10.5.4 Post-Trial Events

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

11.0 TRIAL-SPECIFIC REQUIREMENT(S)

11.1 Trial-Specific Committees

11.1.1 Data Monitoring Committee

A 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 RECORD KEEPING

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

12.1 Case Report Forms (Electronic)

Completed eCRFs are required for each subject who provides a signed informed consent/pediatric assent form.

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

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

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

The PI 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 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.

When a site visit cannot be carried out due to the COVID-19 pandemic, alternative methods of contact (e.g.telephone contact) will be made for subjects who are still under monitoring for safety reporting. Refer also to Section 14.1.

12.2 Record Retention

The investigator agrees to keep the records stipulated in Appendix A and those documents that include (but are not limited to) the trial-specific documents, the identification log of all participating subjects, medical records. Temporary media such as thermal sensitive paper should be copied and certified, source worksheets, all original signed and dated informed consent or informed consent and pediatric assent forms, subject authorization forms regarding the use of personal health information (if separate from the informed consent or pediatric assent forms),

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

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

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

An SAP will be prepared and finalized prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all trial objectives.

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

13.1.1 Analysis Sets

Safety set: the safety set will consist of all subjects who received at least 1 dose of TDV or 9vHPV.

Full analysis set (FAS): the FAS will include all randomized subjects who received at least 1 dose of trial vaccine and for whom valid pre-dosing (Day 0 [M0]) and at least 1 post-dosing measurement have been received for immunogenicity assessments.

Per-protocol set (PPS): the PPS will exclude all subjects seropositive for HPV at Baseline and will include all subjects in the FAS who have no major protocol violations. The major protocol violation criteria will be defined as part of a data review prior to the analysis. The categories of major protocol violations include: (1) not meeting selected entry criteria, (2) receiving the wrong trial vaccine, (3) receiving prohibited therapies, and (4) other major protocol violations that may be identified during data reviews.

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

13.1.2 Analysis of Demographics and Other Baseline Characteristics

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

13.1.3 Immunogenicity Analysis

The primary objective, NI of the immune response to 2 doses of 9vHPV vaccine when concomitantly administered with TDV compared to administration of 9vHPV vaccine alone, will be assessed in terms of GMTs on Day 210 (M7). NI for each HPV type will be concluded if the upper bound of the 95% confidence interval (CI) for the GMT ratio (Group 2/Group 1) is less than the NI margin of 1.5. Overall NI will be concluded if NI requirement is met for all 9 HPV types, therefore no multiplicity adjustment of first type error is needed and 95% CI will be used in each comparison.

Descriptive statistics including 95% CI for the primary and secondary endpoints, including seropositivity rates and GMTs, will be computed by trial group for all available assays at all relevant time points.

An analysis of (co)variance (AN[CO]VA) model on the natural logarithms of titer values will be used to compute the 95% CI of the GMT ratios, with trial group as a factor based on the PPS. A similar, supportive ANCOVA, with trial group as a factor and the natural logarithms of pre-vaccination titers as a covariate may be provided based on the FAS.

Handling of missing data will be described in the SAP.

Potential analyses and/or table summaries may be performed to assess the impact of the COVID-19 pandemic. These may include sensitivity analyses ignoring the protocol-defined visit windows for the PPS subjects impacted by COVID-19.

13.1.4 Safety Analysis

Solicited AEs

Presence and severity (Grade) of solicited local (injection site reactions pain, injection site erythema and injection site swelling) will be collected using diary cards on Day 1 (M0) and Day 90 (M3) for 7 days following each vaccination. In Group 1, reactions on both injection sites (TDV and 9vHPV vaccine) will be collected on Day 1 (M0) and at the TDV injection site on Day 90 (M3). In Group 2, reactions at the 9vHPV vaccine injection site will be collected on Day 1 (M0).

Presence and severity (Grade) of solicited systemic AEs (fever, asthenia, malaise, headache and myalgia) will be collected using diary cards for 14 days following each vaccination. Collection starting on Day 1 (M0) will be for both injection sites and for subjects in Groups 1 and 2, and collection starting on Day 90 (M3) will only be for subjects in Group 1 after the second TDV dose.

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

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

Unsolicited AEs

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

Unsolicited AEs will be coded using MedDRA, and summarized by Preferred Term (PT) and System Organ Class (SOC) for each trial group.

Unsolicited AEs will be summarized as follows: by PT including events with frequency greater than a pre-defined frequency (the percentage will be specified in the SAP); by SOC and PT; by

SOC, PT, and severity; and by SOC, PT, and relationship to the trial vaccine(s). Subjects reporting more than 1 occurrence for the term (level) being summarized will be counted only once.

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

SAEs

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

13.2 Interim Analysis and Criteria for Early Termination

An interim analysis of immunogenicity and safety data is planned when all subjects have completed the Day 210 (M7) visit. This will be reported in an interim CSR. A final CSR will be prepared upon trial completion to include safety data collected up to the end of the trial on Day 360 (M12) and will also include results for the whole trial duration.

Please see Section 7.4 for criteria for early termination.

13.3 Determination of Sample Size

The sample size calculation assumes a significance level of 0.025 (one-sided).

For the primary objective of showing NI of 9vHPV GMTs, the calculation assumes a NI margin of 1.5, a true GMT ratio of 1 between trial groups at Day 210 (M7), and that the natural logarithms of the antibody titers against 9 HPV types are independent normally distributed with standard deviations of 0.95, 0.86, 0.98, 0.91, 0.98, 0.94, 1.09, 1.03, and 0.94. The largest variability 1.09 was assumed and used for sample size calculations for all 9 strains.

A sample size of 307 subjects per group, with approximately 261 evaluable subjects per trial group (adjusted for approximately 15% subjects not evaluable for the immunogenicity assessments), is sufficient to achieve approximately 90% power for showing NI for the primary objective.

Sample size calculations were performed using nQuery Advisor® version 8.

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 designee (clinical research organization) and by the IRB or IEC.

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

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. Alternative monitoring approaches should be used only where allowed by the local Health Authority and when approved by the IRB/IEC. During remote monitoring, the monitor should focus on trial activities that are essential to the safety of trial subjects and/or data reliability.

14.2 Protocol Deviations

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

14.3 Quality Assurance Audits and Regulatory Agency Inspections

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

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.

15.0 ETHICAL ASPECTS OF THE TRIAL

This trial will be conducted with the highest respect for the trial subjects according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the ICH Harmonised Tripartite Guideline for GCP [2]. Each investigator will conduct the trial according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the Investigator" that are listed in Appendix A. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 Institutional Review Board and/or Independent Ethics Committee Approval

IRBs and IECs must be constituted according to the applicable local requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this trial, written notification regarding his or her abstinence from voting must also be obtained.

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

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

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

15.2 Subject Information, Informed Consent/Pediatric Assent, and Subject Authorization

Written consent documents will embody the elements of informed consent/pediatric assent as described in the Declaration of Helsinki [1] and the ICH Tripartite Guidelines for GCP [2] and will be in accordance with all applicable laws and regulations. The informed consent/pediatric assent form, and subject information sheet describe the planned and permitted uses, transfers, and disclosures of the subject's personal health information for the purpose of conducting the trial. The informed consent/pediatric assent form and the subject information sheet further explain the nature of the trial, its objectives, and potential risks and benefits, as well as the date informed consent/pediatric assent is given. The informed consent/pediatric assent form will detail the requirements of the subject and the fact that the subject/subject's LAR is free to withdraw their child at any time without giving a reason and without prejudice to the subject's further medical care.

The investigator should assess the need for re-consent/re-affirmation of consent in situations wherein there has been substantial changes to the subject's status of condition since the original consent. The process should comply with relevant local regulations.

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

The informed consent/pediatric assent form, and subject information sheet must be written in a language fully comprehensible to the prospective subject/subject's LAR. It is the responsibility of the investigator to explain the detailed elements of the informed consent/pediatric assent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject/subject's LAR. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's LAR may provide such consent for the subject in accordance with applicable laws and regulations (e.g., pediatric assent form).

The subject/subject's LAR must be given ample opportunity to: (1) inquire about details of the trial and (2) decide whether or not to (allow the child to) participate in the trial. If the subject, or subject's LAR, determines he, she or their child will participate in the trial, then the informed consent/pediatric assent form must be signed and dated by the subject/the subject's LAR, at the time of consent and prior to the subject entering into the trial. The subject or the subject's LAR should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent/pediatric assent at the time of consent and prior to the subject entering into the trial; however, the sponsor may allow a designee of the investigator to sign to the extent permitted by applicable law.

Once signed, the original informed consent/pediatric assent form, and subject information sheet will be stored in the investigator's site file. The investigator must document the date the subject/subject's LAR signs the informed consent/pediatric assent form in the subject's medical record and eCRF. Copies of the signed informed consent/pediatric assent form, the signed subject

authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

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

15.3 Subject Confidentiality

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

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit its monitor or designee, representatives from any regulatory authority (e.g., FDA, MHRA, PMDA), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, electrocardiogram (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/subject's LAR as part of the informed consent/pediatric assent form process (see Section 15.2).

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

15.4 Clinical Trial Registration, Publication and Disclosure Policy

15.4.1 Clinical Trial Registration

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

15.4.2 Clinical Trial Results Disclosure

Takeda disclosure policy aims to comply with the clinical trial data disclosure requirements of all relevant regions. The sponsor will post the results of this clinical trial regardless of outcome, on

publicly accessible websites such as ClinicalTrials.gov and/or EudraCT, as required by applicable laws and/or regulations.

Completion of trial corresponds to the date on which the final subject was examined or received an intervention for the purpose of final collection of data (usually correspond to Last Subject Last Visit).

In case the deadline for results disclosure cannot be met, an application for extension with scientific justification will be initiated.

15.4.3 Publication of Trial Results

The results of this trial are expected to be published in a peer-reviewed scientific journal. Publication of trial results will follow Takeda publication policies, applicable international standards and guidelines for good publication practice, applicable laws, and/or regulations.

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 that will assist in the protocol.
3. Ensure that trial related procedures, including trial specific (non-routine/non-standard panel) screening assessments, are NOT performed on potential subjects prior to the receipt of written approval from relevant governing bodies/authorities.
4. Ensure that all colleagues and employees assisting in the conduct of the trial are informed of these obligations.
5. Secure prior approval of the trial and any changes by an appropriate IRB/IEC that conforms to 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/pediatric assent, as outlined in ICH and local regulations, are met.
8. Obtain valid informed consent/pediatric assent from the LAR of each subject/each subject who participates in the trial, and document the date of consent in the subject's medical chart. Valid informed consent/pediatric assent form is the most current version approved by the IRB/IEC. Each informed consent/pediatric assent form should contain a subject authorization section that describes the uses and disclosures of a subject's personal information (including personal health information) that will take place in connection with the trial. If an informed consent/pediatric assent 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 LAR.
9. Prepare and maintain adequate case histories of all persons entered into the trial, including eCRFs, hospital records, laboratory results, etc, and maintain these data for a minimum of 2 years following notification by the sponsor that all investigations have been discontinued or that the regulatory authority has approved the marketing application. The investigator should contact and receive written approval from the sponsor before disposing of any such documents.
10. Allow possible inspection and copying by the regulatory authority of GCP-specified essential documents.

11. Maintain current records of the receipt, administration, and disposition of sponsor-supplied vaccines, and return all unused sponsor-supplied vaccines to the sponsor.
12. Report AEs to the sponsor promptly. In the event of an SAE, notify the sponsor within 24 hours.
13. Review and provide a signature as approval of the content of the clinical study report, if required.

Appendix B Investigator Consent to Use of Personal Information

Takeda will collect and retain personal information of the investigator, including his or her name, address, and other personally identifiable information. In addition, investigator's personal information may be transferred to other parties located in countries throughout the world (eg, the United Kingdom, USA, 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.

Signature Page for DEN-308 Protocol Amendment 2, Version 5.0, 03 March 2021
Title: Immunogenicity and Safety of TDV and 9vHPV in Subjects Aged ≥9 to <15 Yea

Approval	[redacted]
Approval	[redacted]
Approval	[redacted]
Approval	[redacted]

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