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

SAP Approve Date: 25 August 2020

Certain information within this Statistical Analysis Plan has been redacted (ie, specific content is masked irreversibly from view with a black bar) to protect either personally identifiable information or company confidential information.

STATISTICAL ANALYSIS PLAN

STUDY NUMBER: DEN-308

A Phase 3, Open-Label, Randomized Trial to Investigate the Immunogenicity and Safety of the Co-administration of a Subcutaneous Tetravalent Dengue 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

Version**:** 1.0

Date**:** 25 August 2020

Prepared by:

[redacted]

Based on:

Protocol Version: 3.0

Protocol Date: 10 August 2020

1.1 Approval Signatures

Electronic signatures can be found on the last page of this document.

2.0 TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

3.0 LIST OF ABBREVIATIONS

9vHPV	Recombinant 9-valent human papillomavirus vaccine
AE	Adverse event
ANCOVA	Analysis of covariance
ANOVA	Analysis of variance
COVID-19	Corona Virus Disease 2019
CRO	Contract research organization
DENV	Wild type dengue virus
eCRF	electronic Case Report Form
FAS	Full Analysis Set
GMT	Geometric mean titers
GSD	Geometric standard deviation
HPV	Human Papillomavirus
IgGBA	Immunoglobulin G binding assay
IM	Intramuscular
IP	Investigational Product
LLOD	Lower limit of detection
LLOQ	Lower limit of quantification
LS	Least square
M0, 1, 3, 4, 6, 9, 12	Month 0, 1, 3, 4, 6, 9, 12
MedDRA	Medical Dictionary for Drug Regulatory Activities
MNT_{50}	Microneutralization test 50%
NI	Non-inferiority
PPS	Per-Protocol Set
PT	Preferred Term
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis System
SC	Subcutaneous
SOC	System Organ Class
TDV	Tetravalent dengue vaccine candidate
WHODrug	World Health Organization Drug Dictionary

4.0 OBJECTIVES

4.1 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 adminstered alone.

4.2 Secondary Objectives

Immunogenicity:

- To describe the immune response to HPV (in terms of seroresponse) in subjects administered 2 doses of 9vHPV vaccine, 1 co-adminstered 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.

4.3 Study Design

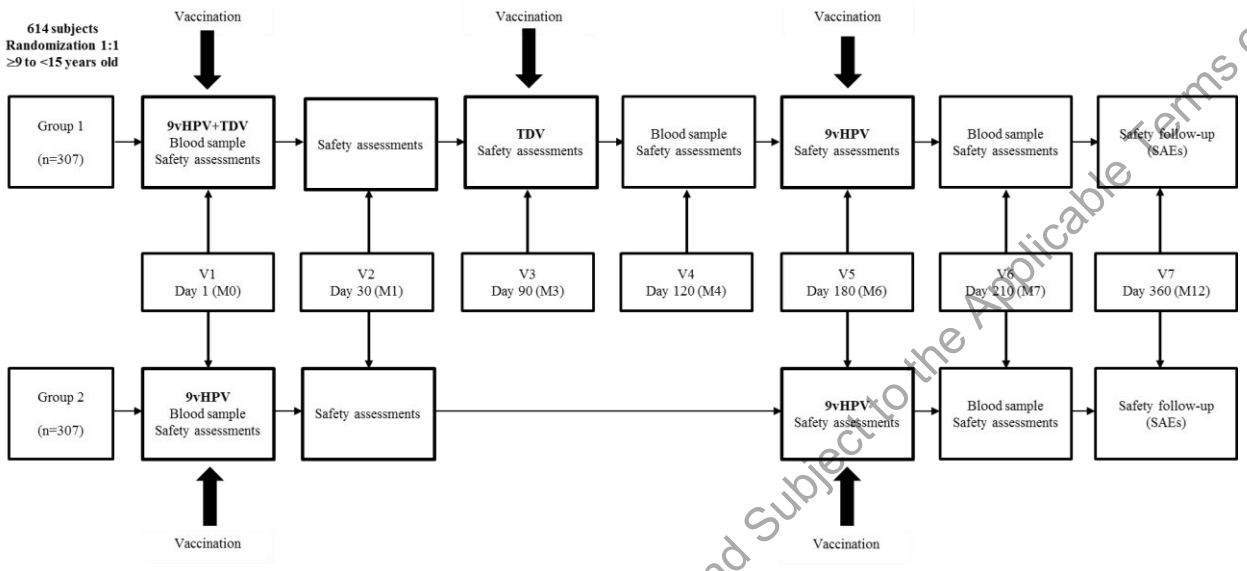
This is a phase 3, open-label, randomized, multicenter trial in 614 healthy subjects aged ≥9 to <15 years in endemic areas for dengue, to investigate the immunogenicity and safety of the co-administration of TDV and 9vHPV vaccine vs. 9vHPV vaccine alone. Subjects will be randomized equally (1:1 ratio) to 1 of the following 2 trial groups (307 subjects per 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 vaccine will be injected into opposite arms. All subjects will be followed-up for 6 months after 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 4.a. A schedule of trial procedures is provided in Appendix A.

Figure 4.a Schematic of Trial Design



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 Group 1 and Group 2 will be collected at pre-first trial vaccination Day 1 [Month(M) 0] and 1 month post second 9vHPV vaccination (Day 210 [M7]).

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

Safety evaluation (all subjects):

- Diary cards will be distributed to all subjects' leaglly authorized representatives (LAR) for the recording of:
  - Solicited local (injection site) reactions for 7 days following vaccination (day of vaccination + 6 subsequent days) on Day 1 (M0) and Day 90 (M3). Collection starting on Day 1 (M0) will be for subjects in Groups 1 (for both injection sites) and 2, and collection starting on Day 90 (M3) will be for subjects in Group 1 after the second TDV dose. Adverse events 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 subsequent days) on Day 1 (M0) and Day 90 (M3). Collection starting on Day 1 (M0) will be for subjects in Groups 1 and 2, and collection starting on Day 90 (M3) will only be for subjects in Group 1 after second TDV dose. Adverse events will include: fever (defined as body temperature ≥38.0ºC [≥100.4ºF]), headache, asthenia, malaise, and myalgia.
- Unsolicited AEs will be collected by interview and recorded for all subjects for 28 days following vaccination (day of vaccination + 27 subsequent days) on Day 1 (M0) (Group 1 and 2), and Day 90 (M3) (Group1).
- Serious adverse events (SAEs), AEs leading to subject discontinuation or withdrawal will be collected for the trial duration.

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

5.0 ANALYSIS ENDPOINTS

5.1 Primary Endpoint

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

5.2 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 (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 clincal likelihood of HPV infection and positive or negative status by previous versions of IgGBA or equivalent assay. The lower limits of quantification and serostatus cut-offs for each of the 9 vaccine HPV types are shown in Table 5.a.

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.

Table 5.a Immunoglobulin G Binding Assay Limits of Quantification and Serostatus Cut-offs for 9vHPV Types

HPV Type	IgGBA Lower Limit of Quantification (mMU[(a)]/mL)	IgGBA Serostatus Cut-off (mMU[(a)]/mL)
HPV 6	2	9
HPV 11	2	6
HPV 16	4	5
HPV 18	3	5
HPV 31	2	3
HPV 33	2	4
HPV 45	1	3
HPV 52	1	5
HPV 58	2	5

(a) mMU=milli-Merck units

Safety:

- Frequency and severity of solicited local (injection site[s]) AEs for 7 days (day of vaccination + 6 subsequent days) (Group 2 and collected at each injection site in Group 1) and solicited systemic AEs for 14 days (day of vaccination + 13 subsequent 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 subsequent 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).

6.0 DETERMINATION OF SAMPLE SIZE

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 endpoint with a significance level of 0.025 (one-sided).

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

7.0 METHODS OF ANALYSIS AND PRESENTATION

7.1 General Principles

This statistical analysis plan (SAP) was developed based on the information provided in Protocol DEN-308, Version 3.0, dated 10 August 2020 [1] and on the International Conference on Harmonization (ICH) E3 [2] and E9 [3] Guidelines. This document will provide further details regarding the definition of the analysis variables and analysis methodology used to address all trial objectives.

All statistical outputs will be generated using statistical analysis system SAS Version 9.4 or later.

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.

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 (e.g. protocol deviation review, protocol amendment and statistical analysis plan [SAP] amendment) will be documented in the data access management plan, and will be independent of unblinded data review.

7.1.1 Data Presentation

Summary tables for categorical variables will display both frequencies and percentages. For those categorical variables with defined categories in the eCRF, all possible categories will be displayed, even if the subject count is zero. For any other categorical variables recorded (eg, category of AE or medication/vaccination), only categories with at least 1 subject count will be displayed. Percentages will be presented with 1 decimal place (eg, 80.3%).

Summary tables for continuous variables will display the number of subjects with non-missing values, means or geometric means, medians, SD or geometric standard deviations (GSD), and minimum and maximum values. Minimum and maximum values will be presented with the same number of decimal places as the recorded data. Means, geometric means, and medians will be presented with 1 more decimal place than the recorded data. SD will be presented with 2 more decimal places than the recorded data.

Summaries for selected immunogenicity and safety variables may also include CI around parameter estimates (means or percentages). The CI will be presented with the same number of decimal places as the parameter estimate itself.

All collected data will be displayed in the listings sorted by trial group, by site number, by subject number, and by date/time of the recorded event if applicable (eg, date/time of vaccination, date/time of blood draw, date/time of AE). Screen failures data will be grouped and listed separately.

In all outputs, trial groups will be labeled as:

- Group 1: 9vHPV+TDV;
- Group 2: 9vHPV.

7.1.2 Study Day, Baseline and Analysis Window Definitions

Study Day 1 (M0) is defined as the date of the first vaccination, as recorded on the eCRF vaccination form. Other Study Days are defined relative to Study Day 1 (M0), with Day -1 being the day prior to Day 1 (M0).

Baseline is defined as the last non-missing measurement taken before the first trial vaccination. Where time is available, the time of the measurement must be prior to the trial vaccination time. Day 1 (M0) measurements taken after the first trial vaccination time are considered as post-Baseline values.

A windowing convention for immunogenicity and safety (vital signs) data will be used to determine the analysis value of a variable at a given trial visit. Following the schedule of trial procedures (Appendix A), the analysis visit windows for each visit will be calculated relative to the day on which each trial dose was administered (Day 1 [M0], Day 90 [M3] and Day 180 [M6]). If several measurements of a variable are obtained for a given subject within the same visit window, the measurement taken at the date that is closest to the scheduled visit date will be used. If the 2 measurements are equidistant from the scheduled visit, the later date will be used. Both scheduled and unscheduled visits will be considered equally.

The analysis windows are displayed in Table 7.a below.

Table 7.a Analysis Visit Windows

Visit	Study Day (Month)	Scheduled Vaccination	Analysis Visit Windows		
			Safety Set (Vital Signs)	Full Analysis Set	Per-Protocol Set
V1	Day 1 (M0)	Dose 1 Group 1: 9vHPV+TDV Group 2: 9vHPV	Prior [≤1 day] [a] to Dose 1	Prior [≤1 day] [a] to Dose 1	Prior [≤1 day] [a] to Dose 1
V2	Day 30 (M1)		2 – 60 days [b] after Dose 1	Not applicable (no blood draw)	Not applicable (no blood draw)
V3	Day 90 (M3)	Dose 2 Group 1: TDV	61 – 115 days [b] after Dose 1 and/or Prior [≤1 day] [a] to Dose 2 (TDV) [c]	Not applicable (no blood draw)	Not applicable (no blood draw)
V4	Day 120 (M4)		2 – 60 days [b] after Dose 2 (TDV) [c] or 116 – 150 days [b] after Dose 1 [d]	2 – 75 days [b] after Dose 2 (TDV) [c] or 2 – 165 days [b] after Dose 1 [d]	29 – 37 days [b] after Dose 2 (TDV) [c] or 119 – 127 days [b] after Dose 1 [e]
V5	Day 180 (M6)	Dose 2 Group 2: 9vHPV Dose 3 Group 1: 9vHPV	61 – 115 days [b] after Dose 2 (TDV) [c] or 151 – 205 days [b] after Dose 1 [d] and/or Prior [≤1 day] [a] to Dose 2/3 (9vHPV)	Not applicable (no blood draw)	Not applicable (no blood draw)
V6	Day 210 (M7)		2 – 105 days [b] after Dose 2/3 (9vHPV) or 116 – 195 days [b] after Dose 2 (TDV) [c] or 206 – 285 days [b] after Dose 1 [d]	≥2 days [b] after Dose 2/3 (9vHPV) or ≥76 days [b] after Dose 2 (TDV) [d] or ≥166 days [b] after Dose 1 [d]	29 – 37 days [b] after Dose 2/3 (9vHPV)
V7	Day 360 (M12)		≥106 days [b] after Dose 2 (9vHPV) or ≥196 days [b] after Dose 2 (TDV) [c] or ≥286 days [b] after Dose 1 [d]	Not applicable (no blood draw)	Not applicable (no blood draw)

(a) Blood draw for immunogenicity assessments and assessment of vital signs must be prior to the vaccination scheduled for the same visit, and where time is available, the time of the blood/vital signs collection must be prior to the vaccination time. Day 1 (M0) measurements taken after the first trial vaccination time are considered post-Baseline values.
(b) Number of days after the visit is calculated with 1 day increment. For example, for V2 number of days after V1 is calculated as [Date of V2] – [Date of V1] + 1 (day).
(c) Applies to subjects in Group 1 only.

(d) Applies to subjects in Group 2 and subjects in Group 1 who did not receive second/third dose of TDV/9vHPV at V3/V5.
(e) Applies to subjects in Group 2 only.

7.1.3 Handling of Missing Data

Data will be presented in the listings as reported. For the summaries and analyses, following conventions apply.

Missing Immunogenicity Data

Dengue neutralizing antibody titers (MNT_{50}) that are below the lower limit of detection (LLOD, 10) will be imputed with a value of 5 (half of the LLOD). Reported values greater than or equal to the LLOD and less than the lower limit of quantification (LLOQ, which differs between serotypes) will be imputed with the mid-point between the LLOD and LLOQ. For example, given a LLOQ of 68 for a serotype, all values ≥10 and <68 will be imputed as 39 for this serotype.

Anti-HPV titers (IgGBA) that are below the LLOQ as listed in Table 5.a will be imputed with a value half of the pre-specified LLOQ.

No imputation method will be used for missing immunogenicity data and all analyses will be based on complete records only.

Missing or Partial Dates of Unsolicited AE

Missing and partial unsolicited AE start dates will be imputed only to determine the temporal relationship between the start date of the event and the dose date of the most appropriate vaccination that the AE should be temporally allocated with (ie, Vaccination 1, 2 or 3).

The following rules apply when determining the temporally allocated vaccination:

- If the AE start and end dates are both completely missing, the AE will be allocated with the first trial vaccination;
- If at least the month and/or year of AE start is/are available, the AE will be allocated with the latest vaccination that occurred prior to AE start date;
- If the AE start date is completely missing, or if the available start date information is insufficient to distinguish between the two (Group 2) or three (Group 1) trial vaccinations, but a partial AE end date (ie, month and/or year) is available, the AE end date will be assessed and the AE will be allocated with the vaccination after which the ion event ends. This is based on the assumption that any AE starting after Vaccination 1 or 2 and ongoing on the day of Vaccination 2 or 3 would be identified during the clinical assessments that are performed before administration of the second (Group 2) or third dose (Group 1) trial vaccination. If partial end date information indicates possible allocation with multiple trial vaccinations, the AE will be allocated with the first trial vaccination.

Missing AE Severity or Relationship to Investigational Products (IPs)

Missing AE severity (mild/moderate/severe) and missing AE relationship to IP (related/not related) will be handled using the conservative approach:

- unsolicited AE with missing severity will be considered as 'severe',
- solicited systemic or unsolicited AE with missing relationship will be considered as 'related'.

No other imputation for missing AE data will be implemented.

Missing or Partial Dates for Medications or Vaccines

Missing and partial dates for a medication/vaccine will be assessed, only to distinguish between a prior or concomitant medication/vaccine. A medication will be considered prior only if the partial end date indicates that it was stopped before the first trial vaccination. A vaccine will be considered prior only if the partial vaccination date indicates that it was given before the first trial vaccination. In all other cases medications or vaccines will be considered concomitant.

Missing End Dates of Medical History/Concurrent Medical Conditions

In case the "End Date" or "End Date Unknown" fields are missing on the medical history/ concurrent medical conditions form of the eCRF and from the partial date it can't be concluded that the event is clearly a medical history, the event will be considered a concurrent medical condition.

7.1.4 Handling of Implausible Values

Data outside the plausible ranges as defined in Table 7.b will be excluded from analyses, but the data will be presented as recorded and flagged in data listings.

Table 7.b Plausible Data Ranges

	Parameter	Plausible range
Solicited AE	Swelling	≤ 500 mm
	Erythema	≤ 500 mm
	Body Temperature [(a)]	32 – 43°C
Vital Signs	Height	110 – 210 cm
	Weight	20 – 200 kg
	Heart Rate	40 – 200 beats/min
	Systolic Blood Pressure	70 – 180 mmHg
	Diastolic Blood Pressure	30 – 120 mmHg

(a) Also applicable to body temperature measurements collected as vital signs.

7.2 Analysis Sets

All Screened: All subjects who signed the informed consent, regardless of whether subjects were screen failures.

Randomized Set: All randomized subjects, regardless of whether any dose of the IPs was received.

Summary tables generated for the Randomized Set will present trial groups "as randomized", ie, according to the combination of IPs a subject was designated to receive, which may be different from the IPs the subject actually received. For example, a subject randomized to 9vHPV group (Group 2) but vaccinated with both 9vHPV and TDV (Group 1) will be analyzed in the 9vHPV (Group 2).

Safety Set: All randomized subjects who received at least 1 dose of IPs.

All summaries generated for the Safety Set will present trial groups "as vaccinated", ie, according to the combination of IPs the subject actually received rather than to which he/she was randomized. For example, a subject randomized to 9vHPV group (Group 2) but vaccinated with both 9vHPV and TDV (Group 1) will be analyzed in the 9vHPV+TDV group (Group 1). Subjects who received a combination of IPs that was not planned for any trial group (if any) will be considered in a separate group (eg, only 9vHPV administered on Day 1 [M0] and TDV administered on Day 90 [M3]). Data for this group, labelled as "Unplanned IPs sequence", will be displayed in selected summaries and in all listings and subject mappings generated for the Safety Set.

Full Analysis Set (FAS): All randomized subjects who received at least 1 dose of IPs and for whom both valid pre-dose (Baseline) and post-dose measurement are available for HPV immunogenicity assessments.

Summary tables generated for the FAS will present trial groups "as randomized".

Per–Protocol set (PPS): the PPS will exclude all subjects seropositive for HPV at Baseline and will include all subjects from the FAS who have no major protocol violations.

Major protocol violations are defined as deviations from the protocol that could potentially have a significant impact on the immunogenicity results of a subject. These violations will be identified via programming and/or a data review prior to the final analysis, using criteria as escribed in Table 7.c.

Other major protocol deviations may be identified during data reviews of the data listings and deviation logs throughout the trial. Any changes to PPS exclusion criteria after approval of the SAP will be documented separately and approved prior to performing the final analysis.

Summary tables generated for the PPS will present trial groups "as randomized".

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 maybe provided based on the FAS. The reasons for exclusion of subjects from analysis sets will be summarized by trial group for the Randomized Set.

Analyses based on the Safety Set (except AEs), FAS and PPS sets will only include measurements obtained following the analysis visit windows defined in Table 7.a.

Table 7.c Criteria for Exclusion of Subjects from PPS

Criteria for Exclusion	Method of Identification
Not receiving at least 1 dose of IP [(a)]	Programmatically using dosing data
Not providing a valid pre-dose (Baseline) and at least 1 post-dose measurement for HPV immunogenicity assessment [(b)]	Programmatically using immunogenicity data
Subjects seropositive [(c)] to any serotype of HPV at Baseline (Day 1 [M0])	Programmatically using immunogenicity data
Subject meets any of the exclusion criteria	Through protocol deviation review, programmatically using eCRF-recorded data
Not receiving both 9vHPV Vaccination(s) 1 (Day 1 [M0]) and Vaccination 2 (Day 180 [M6])	Programmatically using dosing data
Receiving 9vHPV Vaccination 2 out of the visit window (ie, outside Day 180 [-15/+25 days])	Programmatically using dosing data
Randomization Errors: Receiving vaccination different from which subject was randomized to	Programmatically using dosing/IWRS data
Product preparation error	Through protocol deviation review
Use of prohibited medications/vaccines	Identified by clinical science review of eCRF-recorded medication/vaccines data

(a) Subjects with this deviation will be excluded from the Safety Set, and thus also from the FAS and PPS.
(b) Subjects with this deviation will be excluded from the FAS, and thus also from the PPS.
(c) See Table 5.a for cut-offs.

7.3 Disposition of Subjects

Trial information will be presented for all screened subjects including: the date the first subject signed the informed consent form, the date of the first subject's first visit, the date of last subject's last visit/contact, the date of first subject's first vaccination, the date of last subject's first vaccination, the date of first subject's second TDV vaccination, the date of first subject's second 9vHPV vaccination, the date of last subject's second 9vHPV vaccination and the date of last subject's last procedure for collection of data for the primary endpoint (ie, date of last blood sample taken for HPV assessment on Day 210 [M7]). In addition, details will be provided, where applicable, for versions of: the Medical Dictionary for Regulatory Activities (MedDRA), the World Health Organization Drug Dictionary (WHODrug), and the SAS used for analyses.

The randomization eligibility summary for all screened subjects will include: the number of screened subjects, the number of subjects eligible for randomization, the number of subjects not eligible for randomization and the primary reason(s) for ineligibility for randomization. The number of screen failures and their characteristics will also be summarized.

Disposition summary for all randomized subjects will include:

- Number of randomized subjects by site;

- Number of randomized subjects and number of subjects randomized but not dosed (including the reason);
- Number of subjects completing the vaccination regimen/trial visits;
- Number of subjects who prematurely discontinued the vaccination regimen/trial (IPs or trial withdrawals);
- Primary reason(s) for premature discontinuation of the vaccination regimen/trial.

Significant protocol deviations will be summarized by trial group for all randomized subjects.

Number of subjects in analysis sets will also be provided as a separate summary by trial group.

An additional listing and summary table may be provided including all protocol deviations (significant and non-significant) related to the Corona Virus Disease 2019 (COVID-19) pandemic, if applicable for this trial.

7.4 Demographic and Other Baseline Characteristics

Age, gender, ethnicity, race, and other Baseline characteristics will be summarized descriptively for the Randomized Set, Safety Set, FAS and PPS. These summaries will include baseline seropositivity status for dengue (seropositive [reciprocal neutralizing titer ≥10 for at least 1 dengue serotype] or seronegative [reciprocal neutralizing titer <10 for all dengue serotypes]), baseline seropositivity status for each and multiple dengue serotypes, and baseline seropositivity status for each and multiple serotypes of HPV (seropositive is defined as anti-HPV titers greater or equal to the prespecified cut-offs as listed in Table 5.a).

7.5 Medical History and Concurrent Medical Conditions

A medical history is defined as any significant condition/disease that stopped at/or prior to administration of the first dose of IP. A concurrent medical condition is defined as any significant condition/disease that is ongoing at the time that the first dose of IP is administered.

Medical history and concurrent medical conditions will be coded using the current version of the MedDRA coding system. Summary tables for each trial group will be provided by System Organ Class (SOC) and Preferred Term (PT) based on the Safety Set.

7.6 Medication History and Concomitant Medications

A prior medication/vaccine (history) is any medication/vaccine for which intake was stopped before administration of the first dose of IP. A concomitant medication/vaccine is any medication/vaccination ongoing at the time of the first dose of IP or taken/administered on/after the first dose of IP.

Medication history, vaccination history, concomitant medications, and concomitant vaccines will be coded using the current version of WHO Drug.

Summary tables for medication history and concomitant medications will be provided for each trial group by Anatomical Therapeutic Chemical class level 2 name and preferred medication

name. Vaccination history and concomitant vaccines will be summarized for each trial group using the vaccine type and name as recorded in the eCRF. Summary tables will be provided for the Safety Set.

7.7 Investigational Products Exposure and Compliance

The Investigator will record in the eCRF all injections of the IPs given to the subject. A summary of IP compliance will be presented for the Safety Set. This summary will include: the number and percentage of subjects who received all doses of IP; the number and percentage of subjects who only received the first dose of IP; and the number and percentage of subjects who only received the first two doses of IP (Group 1 only). This summary will be prepared by trial group, including a separate group of subjects who received unplanned IP sequence (if any).

Trial follow-up is defined as the time period between the first trial vaccination and the end of the trial, inclusive. Follow-up duration will be summarized by trial group for the Safety Set as a continuous variable (n, mean, median, SD, minimum and maximum), also as a categorical variable (frequency and percentage) as in Table 7.d below. The duration of follow-up will be calculated as end of trial date – vaccination date (first, second or third, respectively) + 1 day.

Table 7.d Duration of follow-up

After first vaccination (Vaccination 1 [9vHPV] – Group 1 and Group 2)	**After second vaccination** (Vaccination 2 [TDV] – Group 1 only)	**After second/third vaccination** (Vaccination 3 [9vHPV] – Group 1, Vaccination 2 [9vHPV] – Group 2)
1-30 days	1-30 days	1-30 days
31-90 days	31-90 days	31-90 days
91-120 days	91-120 days	91-120 days
121-180 days	121-180 days	121-180 days
181-360 days	181-270 days	≥ 181 days
≥ 361 days	≥ 271 days	

7.8 Efficacy Analysis

Not applicable.

7.9 Pharmacokinetic/Pharmacodynamic Analysis

Not applicable.

7.10 Other Outcomes

Descriptive Summaries

Descriptive statistics will be provided for the primary and secondary immunogenicity endpoints by trial group (if applicable).

For HPV antibody titers (IgGBA)/ dengue antibody titers (MNT_{50}) these will include:

- Number of subjects with non-missing assessment, GMT with 95% CI, GSD, median, minimum, and maximum. The GMT, 95% CI and GSD will be calculated as the anti-logarithm transformation of the means, 95% CI and SDs of the log-transformed titers.

For seropositivity of HPV virus and dengue virus these will include:

- Number and percentage of seropositive subjects and corresponding 95% CIs calculated by the exact (Clopper-Pearson) method [4].

Graphical Presentations

Graphical presentations for immunogenicity endpoints will be provided by trial group (if applicable) and will include:

- Line plots of GMTs and its corresponding 95% CIs;
- Reverse cumulative distribution curves of antibody titers;
- Bar graphs presenting the percentage of seropositive subjects and the 95% CIs.

Details of the planned analyses and populations used for immunogenicity endpoints is summarized as in Table 7.e below.

Table 7.e Planned Analyses and Populations for Immunogenicity Endpoints

	Endpoint			Planned Analyses and Populations		
Vaccine	**Variable**	**Time Point**	**Endpoint Type**	**Descriptive Summaries**	**Graphical Presentations**	**Pairwise Comparisons[a]**
9vHPV	GMT [a]	Day 210	Primary	PPS, FAS	PPS	PPS, FAS
	Seropositivity rate	Day 210	Secondary	PPS, FAS	PPS	
Dengue	GMT [b]	Day 120	Secondary	PPS, FAS	PPS	
	Seropositivity rate [b][c]	Day 120	Secondary	PPS, FAS	PPS	

(a) Immunogenicity for each HPV serotype will be summarized /analyzed for: HPV-6, HPV-11, HPV-16, HPV-18, HPV-31, HPV-33, HPV-45, HPV-52 and HPV-58.
(b) Immunogenicity for each dengue serotype will be summarized /analyzed for: DENV-1, DENV-2, DENV-3, and DENV-4.
(c) Immunogenicity for multiple dengue serotypes will be summarized in the following categories: Monovalent, Bivalent, Trivalent, Tetravalent, at least Bivalent, at least Trivalent and Tetravalent. For graphical presentation, only at least Trivalent and Tetravalent will be included.

7.10.1 Primary Immunogenicity Endpoint

The primary immunogenicity endpoint for this trial is GMTs for HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58 on Day 210. This endpoint will be used to evaluate the NI of co-administration of 9vHPV and TDV (Group 1) vs administration of 9vHPV alone (Group 2).

A descriptive summary of the primary immunogenicity endpoint will be provided for each trial group. Geometric mean titer ratio for primary comparison (Group 2/ Group 1) will be based on

an analysis of variance (ANOVA) model, which includes the log-transformed value of titer as the dependent variable, and trial group as a factor. The geometric mean, geometric mean titer ratio and 95% CIs are presented in anti-log values of least squares means (LS means) estimated from the ANOVA model. Overall NI of the immune response to 2 doses of 9vHPV when co-administered with TDV compared to administration of 9vHPV alone will be concluded if the upper bound of the 95% CI is less than NI margin of 1.5 for all 9 HPV serotypes. All of these evaluations are considered co-primary, therefore no multiplicity adjustment of the 5% significance level is needed.

The primary immunogenicity analysis will be performed using the PPS. A supportive analysis using an analysis of covariance (ANCOVA) model with trial group as factor and the natural logarithms of pre-vaccination (Baseline) titers as a covariate will be provided using the FAS. Descriptive summaries will be provided for both the PPS and FAS.

Additional exploratory subgroup analyses in analogy to the primary analysis by dengue baseline seropositivity status will be performed using PPS. Descriptive summaries by dengue baseline seropositivity status and trial group will also be provided.

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

7.10.2 Secondary Immunogenicity Endpoints

Secondary immunogenicity endpoints in this trial are

- Proportion of subjects HPV-naive at Baseline who are seropositive for each of the 9 HPVserotypes on Day 210 (M7) (seropositivity rate).
- GMT of neutralizing antibodies for each of the 4 dengue serotypes on Day 120 (M4).
- Proportion of subjects who are seropositive for each of the 4 dengue serotypes and for multiple (2, 3 or 4) dengue serotypes on Day 120 (M4) (seropositivity rate).

Seropositivity for multiple dengue serotypes will be assessed in following categories:

- for only 1 of the 4 dengue serotypes (monovalent),
- for any 2 of the 4 dengue serotypes (bivalent),
- for any 3 of the 4 dengue serotypes (trivalent),
- for all 4 dengue serotypes (tetravalent),
- for at least 2 dengue serotypes (at least bivalent),
- for at least 3 dengue serotypes (at least trivalent).

As specified in Table 7.e secondary immunogenicity endpoints will be summarized descriptively and graphically based on the PPS. Supportive analyses will be provided based on the FAS.

Additional exploratory subgroup analyses on secondary immunogenicity endpoints by dengue baseline seropositivity status will be performed using PPS.

7.10.3 Additional Immunogenicity Endpoints

Not applicable.

7.11 Safety Analysis

All summaries of safety data will be provided using the Safety Set.

7.11.1 Adverse Events

AE data will be summarized by trial group after each vaccination and after any vaccination.

Solicited local (injection site) and systemic AEs are collected for at least 30 min after each vaccination at the site (in-clinic assessment) and then using diary cards that are provided to the subject. Unsolicited AEs are collected by interview. Subjects will be evaluated for solicited local (injection site) AEs for 7 days (day of vaccination + 6 days), solicited systemic AEs for 14 days (day of vaccination + 13 days), and unsolicited AEs for 28 days (day of vaccination + 27 days), following each vaccination. AEs leading to IP withdrawal or trial discontinuation, and SAEs will be collected throughout the trial from first vaccination (Day 1 [M0]) until the end of the trial (Day 360 [M12]).

Reactogenicity (Solicited AEs)

Solicited local (injection site) AEs include injection site pain, injection site erythema, and injection site swelling; for erythema and swelling, the subject will record the greatest surface diameter in mm but for the summaries and listings these data will be converted to cm. The intensity of erythema and swelling will be derived from the recorded diameters.

Solicited systemic AEs include headache, asthenia, malaise, myalgia, and fever (defined as a body temperature ≥38°C). Fever data will be presented using the proposed temperature increments published by the Brighton Collaboration Fever Working Group [5]. Intensity grades for solicited safety parameters are defined in Appendix B.

For each solicited AE, the number and percentage of subjects reporting an event will be summarized by event intensity at the following time intervals, following each vaccination:

- 30 minutes after each vaccination (in-clinic, assessed by investigator);
- Days 1 – 7 (overall, for local [injection site] AEs) or Days 1 – 14 (overall, for systemic AEs) following each vaccination;
- Days 1 – 7 (daily, for local [injection site] AEs) or Days 1 – 14 (daily, for systemic AEs) following each vaccination;
- Days 1 – 3, Days 4 – 7 (overall, for local [injection site] AEs) or Days 1 – 7, Days 8 – 14 (overall, for systemic AEs) following each vaccination.

Percentages will be calculated based on the number of subjects who received the respective dose of IPs and provided at least 1 record (none, mild, moderate or severe) for this AE in the relevant time interval. For example, subjects reporting solicited AEs (at least 1 non-missing record) for Days 1 – 3 will only be included in denominator for the Days 1 – 3 and Days 1 – 7 summaries, but will be excluded from denominator for Days 4 – 7 summaries. For subjects with more than 1 episode of the same event, the maximum intensity will be used in summaries.

Concomitantly administered vaccines (9vHPV and TDV) will be injected into opposite arms at the first vaccination. Solicited local (injection site) AEs reported after the first vaccination will be summarized by co-administered IPs, as displayed in Table 7.f and by route of administration (IM/SC). Arm (left/right) and Vaccine ID collected on the vaccination page of eCRF for Vaccination 1 will be used to identify which IP corresponds to solicited local (injection site) AEs reported for left and right arm at 30 min (in-clinic) and Day 1 – Day 7 (diary card) assessments.

All solicited local (injection site) AEs are considered as related to the IP. For solicited systemic AEs, the relationship to the IP is assessed by the investigator.

Table 7.f Summaries of solicited local (injection site) AEs following first vaccination

	Group 1 9vHPV+TDV	Group 2 9vHPV
Summary: 9vHPV	9vHPV	9vHPV
Summary: TDV	TDV	

The number and percentage of subjects with solicited systemic AEs will be summarized by relationship to the IP for the following time intervals:

- 30 minutes after each vaccination;
- Days 1 – 14 (overall) following each vaccination.

If a subject reports more than 1 episode of the same event, then the strongest relationship will be included in the summaries: a subject who reported both related and unrelated episodes for the same AE will be counted in the related category.

A summary of the day of first onset of each event and the number of days that subjects reported experiencing each event will be presented following each vaccination. The number of days a subject reported each event is calculated as the total of all days the subject reported the event, regardless of whether the event was reported on consecutive days.

An overview table for solicited AEs will be provided. This will include:

- 30 minutes post-vaccination events (solicited local [injection site] and systemic AEs combined);
- Solicited AEs (solicited local [injection site] and systemic AEs combined);
- Solicited local (injection site) AEs;

- Solicited systemic AEs (overall and by relationship to IP);
- Prolonged solicited AEs (overall and for solicited local [injection site] and systemic AEs separately).

A summary of the first day of onset for each solicited AE and, the number of days the subject reports experiencing the AE will be presented for each vaccination. The number of days a subject reports each event is calculated as the total number of days the subject reports this event, regardless of whether the event was reported on consecutive days.

Persistent/prolonged solicited local (injection site) or systemic AEs continuing on Day 8 and Day 15, respectively, following each trial vaccination will be captured as an AE recorded in the Adverse Event eCRF. These AEs will not be included in the summaries of unsolicited AEs, and will be presented in separate listings. Any solicited local (injection site) or systemic AEs that resolved before 8 days and 15 days, respectively, following each trial vaccination, but recurring at a later time (ie, discontinued), will be recorded as an unsolicited AE on the Adverse Event eCRF.

Unsolicited AEs

Unsolicited AEs will be assessed for 28 days following each vaccination (day of vaccination + 27 days). AEs leading to IP withdrawal or trial discontinuation, and all SAEs will be collected for the duration of the trial: from Day 1 (M0) through Day 360 (M12).

All unsolicited AEs, including SAEs and AEs leading to IP withdrawal or trial discontinuation will be coded using the current version of MedDRA. Summary tables of unsolicited AEs will include the number of events and the number and percentage of subjects who experienced events. Percentages will be calculated based on the number of subjects in the Safety Set who received the respective dose of the IP. Subjects who report more than 1 occurrence for a particular MedDRA term (level) will only be counted once in the summaries. Where relationship or severity is concerned, the AE with the most closely related occurrence or the highest known severity will be counted, following a conservative approach.

Unsolicited AEs collected up to 28 days post-vaccination will be summarized as follows:

- by SOC and PT;
- by SOC and PT including PT events with frequency greater than 2% in any trial group;
- by SOC and PT for IP-related AEs;
- by SOC and PT including PT events with a frequency greater that 2% in any trial group for IP related AEs;
- by SOC, PT, and severity (mild, moderate, severe);
- by SOC, PT, and severity (mild/moderate/severe) for IP related AEs.

SAEs, and AEs leading to IP withdrawal or trial discontinuation will be summarized for the duration of the trial as follows:

- By SOC and PT;
- By SOC and PT for IP related AEs.

The summary of SAEs by SOC and PT after any vaccination, and the summary of AEs leading to IP withdrawal or trial discontinuation by SOC and PT will include a separate group for subjects who received an unplanned IP sequence (if any).

In addition, overview tables by trial group will be generated for unsolicited AEs collected up to 28 days post-vaccination, SAEs and AEs leading to IP withdrawal and/or trial discontinuation including the variables as outlined in Table 7.g.

Table 7.g Overview of Unsolicited Adverse Events

	All AEs (28 days post-vaccination)	SAEs	AEs leading to IP withdrawal and/or trial discontinuation
Relationship to IP	✓	✓	✓
Relationship to trial procedure	✓	✓	✓
Severity	✓	✓	✓
AEs leading to IP withdrawal and/or trial discontinuation	✓	✓	
AEs leading to IP withdrawal	✓	✓	✓
AEs leading to trial discontinuation	✓	✓	✓
SAEs and Non-serious AEs	✓		✓
Deaths	✓	✓	✓

For disclosure of trial results an additional AE table by SOC and PT including PT events with a frequency greater than 2% in any trial group will be provided for all non-serious unsolicited AE up to 28 days post-vaccination, and for all non-serious AEs leading to IP withdrawal and/or trial discontinuation during the entire trial duration. This summary table is need for after any vaccination only and will also include a separate group for subjects who received an unplanned IP sequence (if any).

Subject mappings (a list of subject identification numbers in each category of SOC and PT and each trial group) will be provided for all unsolicited AEs, SAEs and AEs leading to IP withdrawal or trial discontinuation and will also include a separate group for subjects who received an unplanned IP sequence (if any).

7.11.2 Clinical Laboratory Evaluations

Not applicable.

7.11.3 Vital Signs

Vital signs will be measured on Day 1 (M0), Day 30 (M1), Day 90 (M3) – Group 1 only, Day 120 (M4) – Group 1 only, Day 180 (M6), Day 210 (M7) and Day 360 (M12). Summary statistics (number of subjects, mean, SD, median, minimum, and maximum) will be calculated for all observed vital signs and for each vital sign change from Baseline. Summaries will be prepared by trial group and trial visit.

7.11.4 12-Lead ECGs

Not applicable.

7.11.5 Other Observations Related to Safety

Not applicable.

7.12 Interim Analysis

An interim analysis of immunogenicity and safety data is planned when all subjects have completed the Day 210 (M7).

The interim analysis will include descriptive summary tables for demographic and Baseline characteristics, safety data up to Day 210 (M7) as well as the final analysis for the primary and secondary immunogenicity endpoints. The PPS will be defined prior to the Month 7 interim analysis and will be kept unchanged. A clinical study report (CSR) will be provided including the final analyses of immunogenicity data and all available safety data up to Day 210 (M7).

Additional safety data collected up to the end of the trial on Day 360 (M12) will be analyzed after the final database lock and provided as an addendum to the CSR. There will be no re-run of all the previously analyzed TLGs.

7.13 Changes in the Statistical Analysis Plan

The SAP describes additional exploratory subgroup analyses on primary endpoints by baseline dengue seropositivity status and additional analyses/summaries that may be provided to assess the impact of the COVID-19 pandemic in case it becomes applicable for this trial, as compared to the protocol.

8.0 REFERENCES

1. A Phase 3, Open-Label, Randomized Trial to Investigate the Immunogenicity and Safety of the Co-adminstration of a Subcutaneous Dengue Tetravalent Vaccine (Live, Attenuated) (TDV) and an Intramuscular Recombinant 9-Valen Human Papillomarius (9vHPV) Vaccine in Subjects Aged ≥9 to <15 Years in an Endemic Country for Dengue, Takeda Vaccines, Inc., Protocol No. DEN-308, Version 3.0, dated 10 August 2020.
2. ICH Harmonized Tripartite Guideline – Clinical Trial Reports: Structure and Content, E3 (http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/structure-and-content-of-clinical-study-reports.html).
3. ICH Harmonized Tripartite Guideline – Statistical Principles for Clinical Trials, E9 (http://www.ich.org/products/guidelines/efficacy/efficacy-single/article/statistical-principles-for-clinical-trials.html).
4. Clopper CJ and Pearson ES. The use of confidence or fiducial limits illustrated in the case of the binomial. Biometrika. 1934;26: 404-13.
5. Marcy SM, Kohl KS, Dagan R, Nalin D, Blum M, Jones MC, et al. Fever as an adverse event following immunization: case definition and guidelines of data collection, analysis and presentation. Vaccine. 2004;22(5-6): 551-6.

Appendix A Schedule of Trial Procedures

Table 8.a Schedule of Trial Procedures

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 or serum) [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		

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								
Blood collection for immunogenicity testing [i]	Group 1 – Dengue neutralizing antibodies (5 mL)	X			X			
	Group 1 – HPV neutralizing antibodies (5 mL)	X					X	
	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.
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:

   a. 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.

   b. 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.

Appendix B Solicited Local (Injection Site) and Systemic Adverse Events and Severity

Table 8.b Solicited Local (Injection Site) and Systemic AEs

Solicited local (injection site) AEs:	Pain Erythema Swelling
Solicited systemic AEs:	Fever [(a)] Headache Asthenia Malaise Myalgia

(a) Fever is defined as a body temperature ≥38°C (100.4°F) regardless of the method used [5].

Table 8.c Severity of Solicited Safety Parameters

Adverse Event	Severity grade	Severity
Pain at injection site	0	None
	1	Mild: No interference with daily activity
	2	Moderate: Interference with daily activity with or without treatment
	3	Severe: Prevents daily activity with or without treatment
Erythema at injection site[(a)]	0	<25 mm
	1	Mild: ≥25 – ≤50 mm
	2	Moderate: >50–≤100 mm
	3	Severe: >100 mm
Swelling at injection site[(a)]	0	<25 mm
	1	Mild: ≥25 – ≤50 mm
	2	Moderate: >50 – ≤100 mm
	3	Severe: >100 mm
Headache	0	None
	1	Mild: No interference with daily activity
	2	Moderate: Interference with daily activity with or without 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)]	NA	None
	NA	38.0 - <38.5ºC
	NA	38.5 - <39.0ºC
	NA	39.0 - <39.5ºC
	NA	39.5 - <40.0ºC
	NA	40.0 - <40.5ºC
	NA	40.5 - <41.0ºC
	NA	≥41.0ºC

(a) Subjects are to record greatest surface diameter in mm on the diary card.

(b) Fever is defined as a body temperature of ≥38°C regardless of the measurement method [5].

Signature Page for DEN 308 Statistical Analysis Plan, Version 1.0, 25 August 202

Title:

Approval	[redacted]

Document Number: TAK-003-08467 v1.0