Clinical trial results:
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

Summary

EudraCT number	2022-003339-24
Trial protocol	Outside EU/EEA
Global end of trial date	19 July 2022

Results information

Result version number	v1 (current)
This version publication date	01 February 2024
First version publication date	01 February 2024

Trial information

Trial identification

Sponsor protocol code	DEN-308

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04313244
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Takeda Vaccines, Inc.
Sponsor organisation address	40 Landsdowne Street, Cambridge, United States, MA 02139
Public contact	Study Director, Takeda Vaccines, Inc., TrialDisclosures@takeda.com
Scientific contact	Study Director, Takeda Vaccines, Inc., TrialDisclosures@takeda.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	19 July 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 July 2022
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to demonstrate the non-inferiority (NI) of the immune response to 2 doses of 9vHPV vaccine, 1 co-administered with TDV, compared with 2 doses of 9vHPV vaccine administered alone.

Protection of trial subjects:

Each participant signed an informed consent form before participating in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	15 May 2021
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Thailand: 614
Worldwide total number of subjects	614
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	369
Adolescents (12-17 years)	245
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 4 investigative sites in Thailand from 15 May 2021 to 19 July 2022.

Pre-assignment

Screening details:

Healthy participants aged ≥9 to <15 years in endemic areas for dengue were enrolled in this study to receive recombinant 9-valent human papillomavirus vaccine (9vHPV) alone or with tetravalent dengue vaccine (TDV).

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	9vHPV+TDV

Arm description:

Participants received 0.5 mL 9vHPV intramuscularly (IM) and 0.5 mL TDV subcutaneously (SC) once on Day 1 (Month 0) followed by 0.5 mL TDV SC once on Day 90 (Month 3) and 0.5 mL 9vHPV IM once on Day 180 (Month 6).

Arm type	Experimental
Investigational medicinal product name	9vHPV vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL 9vHPV IM administered once on Day 1 (Month 0) followed by 0.5 mL once on Day 180 (Month 6).

Investigational medicinal product name	Dengue Tetravalent Vaccine (TDV)
Investigational medicinal product code	
Other name	TAK-003
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

0.5 mL TDV administered SC once on Day 1 (Month 0) followed by 0.5 mL once on Day 90 (Month 3).

Arm title	9vHPV

Arm description:

Participants received 0.5 mL 9vHPV IM once on Day 1 (Month 0) followed by 0.5 mL 9vHPV IM once on Day 180 (Month 6).

Arm type	Experimental
Investigational medicinal product name	9vHPV vaccine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

0.5 mL 9vHPV vaccine IM will be administered once on Day 1 (Month 0) followed by 0.5 mL 9vHPV

vaccine IM once on Day 180 (Month 6).

Number of subjects in period 1	9vHPV+TDV	9vHPV
Started	307	307
Completed	302	304
Not completed	5	3
Withdrawal of Consent	3	3
Invalid Informed Consent Form (ICF)	1	-
Met Exclusion Criteria	1	-

Baseline characteristics

Reporting groups	
Reporting group title	9vHPV+TDV
Reporting group description:	
Participants received 0.5 mL 9vHPV intramuscularly (IM) and 0.5 mL TDV subcutaneously (SC) once on Day 1 (Month 0) followed by 0.5 mL TDV SC once on Day 90 (Month 3) and 0.5 mL 9vHPV IM once on Day 180 (Month 6).	
Reporting group title	9vHPV
Reporting group description:	
Participants received 0.5 mL 9vHPV IM once on Day 1 (Month 0) followed by 0.5 mL 9vHPV IM once on Day 180 (Month 6).	

Reporting group values	9vHPV+TDV	9vHPV	Total
Number of subjects	307	307	614
Age Categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	11.1	11.3	
standard deviation	± 1.60	± 1.59	-
Gender categorical Units: Subjects			
Female	150	156	306
Male	157	151	308
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	307	307	614
Unknown or Not Reported	0	0	0
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	307	307	614
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	0	0	0
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Region of Enrollment Units: Subjects			
Thailand Thailand	307	307	614
Height Units: centimeters (cm)			
arithmetic mean		148.18	
standard deviation	±	± 11.374	-
Weight Units: kilograms (kg)			

arithmetic mean		44.37	
standard deviation	±	± 14.271	-
Body Mass Index (BMI)			
BMI=weight (kg) / [height (m)]^2			
Units: kilograms per meter square (kg/m^2)			
arithmetic mean		19.88	
standard deviation	±	± 4.762	-

Subject analysis sets

Subject analysis set title	9vHPV+TDV
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

Participants will receive 0.5 mL 9vHPV IM with 0.5 mL TDV SC once on Day 1 (Month 0) followed by 0.5 mL TDV SC once on Day 90 (Month 3) and 0.5 mL 9vHPV IM once on Day 180 (Month 6). This analysis set included all participants with data available for height, weight, and body mass index (BMI) at the Baseline.

Reporting group values	9vHPV+TDV		
Number of subjects	306		
Age Categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean			
standard deviation	±		
Gender categorical			
Units: Subjects			
Female			
Male			
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino			
Not Hispanic or Latino			
Unknown or Not Reported			
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native			
Asian			
Native Hawaiian or Other Pacific Islander			
Black or African American			
White			
More than one race			
Unknown or Not Reported			
Region of Enrollment			
Units: Subjects			
Thailand Thailand			

Height Units: centimeters (cm) arithmetic mean standard deviation	 147.68 ± 12.244		
Weight Units: kilograms (kg) arithmetic mean standard deviation	 44.21 ± 15.913		
Body Mass Index (BMI)			
BMI=weight (kg) / [height (m)]^2			
Units: kilograms per meter square (kg/m^2) arithmetic mean standard deviation	 19.78 ± 4.912		

End points

End points reporting groups

Reporting group title	9vHPV+TDV
Reporting group description:	
Participants received 0.5 mL 9vHPV intramuscularly (IM) and 0.5 mL TDV subcutaneously (SC) once on Day 1 (Month 0) followed by 0.5 mL TDV SC once on Day 90 (Month 3) and 0.5 mL 9vHPV IM once on Day 180 (Month 6).	
Reporting group title	9vHPV
Reporting group description:	
Participants received 0.5 mL 9vHPV IM once on Day 1 (Month 0) followed by 0.5 mL 9vHPV IM once on Day 180 (Month 6).	
Subject analysis set title	9vHPV+TDV
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
Participants will receive 0.5 mL 9vHPV IM with 0.5 mL TDV SC once on Day 1 (Month 0) followed by 0.5 mL TDV SC once on Day 90 (Month 3) and 0.5 mL 9vHPV IM once on Day 180 (Month 6). This analysis set included all participants with data available for height, weight, and body mass index (BMI) at the Baseline.	

Primary: Geometric Mean Titers (GMTs) for Human Papillomavirus (HPV) Types 6, 11, 16, 18, 31, 33, 45, 52, 58

End point title	Geometric Mean Titers (GMTs) for Human Papillomavirus (HPV) Types 6, 11, 16, 18, 31, 33, 45, 52, 58[1]
End point description:	
GMTs for HPV were measured by immunoglobulin G binding assay (IgGBA) assay. HPV-6, HPV-11, HPV-16, HPV-18, HPV-31, HPV-33, HPV-45, HPV-52 and HPV-58 were the types of HPV analyzed. The Per-protocol Set (PPS) excluded all participants seropositive to any HPV type at Baseline and included all participants from the Full Analysis Set (FAS) who had no major protocol violations. Overall number of participants analyzed is the number of participants available for analyses.	
End point type	Primary
End point timeframe:	
Day 210 (Month 7)	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As prespecified in the protocol, only descriptive statistics were planned to be analysed and reported for this endpoint.

End point values	9vHPV+TDV	9vHPV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	237	234		
Units: titer				
geometric mean (confidence interval 95%)				
HPV-6	1633.693 (1465.31 to 1821.43)	1790.986 (1556.08 to 2061.35)		
HPV-11	1342.745 (1225.64 to 1471.04)	1325.192 (1164.58 to 1507.95)		
HPV-16	7777.694 (6989.76 to 8654.45)	7822.564 (6701.83 to 9130.71)		
HPV-18	2309.629 (2075.91 to 2569.66)	2506.309 (2182.67 to 2877.93)		

HPV-31	1690.941 (1529.39 to 1869.55)	1736.943 (1515.05 to 1991.33)		
HPV-33	1138.716 (1019.66 to 1271.67)	1179.469 (1033.66 to 1345.84)		
HPV-45	504.033 (453.46 to 560.24)	584.198 (509.91 to 669.31)		
HPV-52	585.606 (533.44 to 642.87)	561.007 (492.77 to 638.69)		
HPV-58	1163.600 (1060.23 to 1277.05)	1284.504 (1130.63 to 1459.32)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Seropositivity for HPV Types 6, 11, 16, 18, 31, 33, 45, 52 and 58 as Measured by Immunoglobulin G Binding Assay (IgGBA)

End point title	Percentage of Participants with Seropositivity for HPV Types 6, 11, 16, 18, 31, 33, 45, 52 and 58 as Measured by Immunoglobulin G Binding Assay (IgGBA)

End point description:

Seropositive for HPV is defined as anti-HPV titers greater or equal to the prespecified cutoffs for any of the 9 HPV serotypes: HPV-6, HPV-11, HPV-16, HPV-18, HPV-31, HPV-33, HPV-45, HPV-52 and HPV-58, measured by IgGBA. 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. The serostatus cut-offs for the 9 HPV serotypes: HPV-6= 9, HPV-11= 6, HPV-16= 5, HPV-18= 5, HPV-31= 3, HPV-33= 4, HPV-45= 3, HPV-52= 5 and HPV-58= 5. Percentages are rounded off to the nearest decimal point. The PPS excluded all participants seropositive to any HPV type at Baseline and included all participants from the FAS who had no major protocol violations. Overall number of participants analyzed is the number of participants available for analyses.

End point type	Secondary

End point timeframe:

Day 210 (Month 7)

End point values	9vHPV+TDV	9vHPV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	237	234		
Units: percentage of participants				
number (confidence interval 95%)				
HPV-6	100.0 (98.5 to 100.0)	99.1 (96.9 to 99.9)		
HPV-11	100.0 (98.5 to 100.0)	99.1 (96.9 to 99.9)		
HPV-16	100.0 (98.5 to 100.0)	99.1 (96.9 to 99.9)		
HPV-18	100.0 (98.5 to 100.0)	99.1 (96.9 to 99.9)		

HPV-31	100.0 (98.5 to 100.0)	99.1 (96.9 to 99.9)		
HPV-33	100.0 (98.5 to 100.0)	99.1 (96.9 to 99.9)		
HPV-45	100.0 (98.5 to 100.0)	99.1 (96.9 to 99.9)		
HPV-52	100.0 (98.5 to 100.0)	99.1 (96.9 to 99.9)		
HPV-58	100.0 (98.5 to 100.0)	99.1 (96.9 to 99.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: GMTs of Neutralizing Antibodies for Each of the 4 Dengue Serotypes

End point title	GMTs of Neutralizing Antibodies for Each of the 4 Dengue Serotypes[2]

End point description:

GMTs of neutralizing antibodies for each of the 4 dengue serotypes were measured by microneutralization test 50% (MNT50). The four dengue serotypes: DENV-1, DENV-2, DENV-3 and DENV-4. As prespecified in the protocol, the data for this outcome measure was collected and analyzed for participants in the 9vHPV+TDV arm group only. The PPS excluded all participants seropositive to any HPV type at Baseline and included all participants from the FAS who had no major protocol violations. Overall number of participants analyzed is the number of participants available for analyses.

End point type	Secondary

End point timeframe:

Day 120 (Month 4)

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As prespecified in the protocol, the data for this outcome measure was collected and analyzed for participants in the 9vHPV+TDV arm group only.

End point values	9vHPV+TDV			
Subject group type	Reporting group			
Number of subjects analysed	238			
Units: titer				
geometric mean (confidence interval 95%)				
DENV-1	719.1 (577.8 to 895.0)			
DENV-2	1691.4 (1411.0 to 2027.4)			
DENV-3	555.4 (462.8 to 666.6)			
DENV-4	494.3 (420.8 to 580.6)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Solicited Local Adverse Events for 7 Days Following Vaccination by Severity

End point title	Percentage of Participants with Solicited Local Adverse Events for 7 Days Following Vaccination by Severity

End point description:

Solicited local adverse events (AEs) (at injection site) were collected by participants using diary cards within 7 days after vaccination and included: Pain [Grade 0 (no pain), 1 (mild: no interference with daily activity), 2 (moderate: interference with daily activity with or without treatment) and 3 (severe: prevents daily activity with or without treatment)]; erythema and swelling [Grade 0 (<25 millimeters [mm]), 1 (25 - ≤ 50 mm), 2 (>50 - ≤ 100 mm), 3 (> 100 mm)]. Percentages are rounded off to the nearest decimal point. The data for solicited local adverse events after any vaccination are presented. Only those categories with at least 1 participant with event are reported. Safety Set included all randomized participants who received at least 1 dose of IPs.

End point type	Secondary

End point timeframe:

Up to 7 days (Day of vaccination + 6 subsequent days) after each vaccination

End point values	9vHPV+TDV	9vHPV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	307		
Units: percentage of participants				
number (not applicable)				
Pain: Mild	54.1	42.8		
Pain: Moderate	9.5	6.5		
Pain: Severe	0.7	0		
Erythema: Mild	7.5	0		
Erythema: Moderate	0.7	0		
Swelling: Mild	3.3	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Seropositivity for Each of the 4 Dengue Serotypes

End point title	Percentage of Participants with Seropositivity for Each of the 4 Dengue Serotypes[3]

End point description:

Seropositivity is defined as a reciprocal neutralizing antibody titer ≥10 for any of the 4 dengue serotypes. The four dengue serotypes: DENV-1, DENV-2, DENV-3 and DENV-4. As prespecified in the protocol, the data for this outcome measure was collected and analyzed for participants in the 9vHPV+TDV arm group only. Percentages are rounded off to the nearest decimal point. The PPS excluded all participants seropositive to any HPV type at Baseline and included all participants from the FAS who had no major protocol violations. Overall number of participants analyzed is the number of participants available for analyses.

End point type	Secondary

End point timeframe:

Day 120 (Month 4)

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As prespecified in the protocol, the data for this outcome measure was collected and analyzed for participants in the 9vHPV+TDV arm group only.

End point values	9vHPV+TDV			
Subject group type	Reporting group			
Number of subjects analysed	238			
Units: percentage of participants				
number (confidence interval 95%)				
DENV-1	100.0 (98.5 to 100.0)			
DENV-2	99.6 (97.7 to 100.0)			
DENV-3	100.0 (98.5 to 100.0)			
DENV-4	100.0 (98.5 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Seropositivity for Multiple (2, 3 or 4) Dengue Serotypes

End point title	Percentage of Participants with Seropositivity for Multiple (2, 3 or 4) Dengue Serotypes[4]

End point description:

Seropositivity is defined as a reciprocal neutralizing antibody titer ≥10 for any of the 4 dengue serotypes. The dengue virus serotypes are DENV-1, DENV-2, DENV-3 and DENV-4. Seropositive for multiple dengue serotypes were summarized for categories with at least one participant with event: trivalent (seropositive for 3 dengue serotypes), and tetravalent (seropositive for all 4 dengue serotypes). As prespecified in the protocol, the data for this outcome measure was collected and analyzed for participants in the 9vHPV+TDV arm group only. Percentages are rounded off to the nearest decimal point. The PPS excluded all participants seropositive to any HPV type at Baseline and included all participants from the FAS who had no major protocol violations. Overall number of participants analyzed is the number of participants available for analyses.

End point type	Secondary

End point timeframe:

Day 120 (Month 4)

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: As prespecified in the protocol, the data for this outcome measure was collected and analyzed for participants in the 9vHPV+TDV arm group only.

End point values	9vHPV+TDV			
Subject group type	Reporting group			
Number of subjects analysed	238			
Units: percentage of participants				
number (confidence interval 95%)				
Trivalent	0.4 (0.0 to 2.3)			

Tetravalent	99.6 (97.7 to 100.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Solicited Systemic Adverse Events (AEs) for 14 Days Following Vaccination by Severity

End point title	Percentage of Participants with Solicited Systemic Adverse Events (AEs) for 14 Days Following Vaccination by Severity

End point description:

Solicited systemic AEs were collected by participants using diary cards within 14 days after vaccination and included fever, headache, asthenia, malaise, and myalgia. Severity grades were: Grade 0: none, Grade 1: mild (no interference with daily activity), Grade 2: moderate (interference with daily activity with or without treatment), Grade 3: severe (prevents normal daily activity with or without treatment). Fever is defined as body temperature greater than or equal to 38°C (100.4 degrees Fahrenheit [°F]). Only categories with at least one participant with event following any vaccination are reported. Percentages are rounded off to the nearest decimal point. The data for solicited systemic adverse events after any vaccination are presented. Only those categories with at least 1 participant with event are reported. Safety Set included all randomized participants who received at least 1 dose of IPs.

End point type	Secondary

End point timeframe:

Up to 14 days (Day of vaccination + 13 subsequent days) after each vaccination

End point values	9vHPV+TDV	9vHPV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	307		
Units: percentage of participants				
number (not applicable)				
Headache: Mild	20.0	18.0		
Headache: Moderate	3.0	0.7		
Headache: Severe	0.3	0		
Asthenia: Mild	16.7	12.1		
Asthenia: Moderate	2.0	1.0		
Asthenia: Severe	0.3	0		
Malaise: Mild	17.7	10.5		
Malaise: Moderate	2.0	1.3		
Malaise: Severe	0.3	0		
Myalgia: Mild	36.1	27.8		
Myalgia: Moderate	7.9	2.3		
Myalgia: Severe	0.3	0.3		
Fever: 38.0°C-<38.5°C	2.0	0.3		
Fever: 38.5°C-<39.0°C	0.3	0		
Fever: 39.0°C-<39.5°C	0.3	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with any Unsolicited AEs for 28 Days Following Vaccination

End point title	Percentage of Participants with any Unsolicited AEs for 28 Days Following Vaccination

End point description:

An AE is defined as any untoward medical occurrence in a clinical investigation participant administered a study vaccine; it does not necessarily have to have a causal relationship with study vaccine administration. Percentages are rounded off to the nearest decimal point. The data for unsolicited adverse events after any vaccination are presented. Safety Set included all randomized participants who received at least 1 dose of IPs.

End point type	Secondary

End point timeframe:

Up to 28 days (Day of vaccination + 27 subsequent days) after each vaccination

End point values	9vHPV+TDV	9vHPV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	307		
Units: percentage of participants				
number (not applicable)	8.8	2.6		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Serious Adverse Events (SAEs)

End point title	Percentage of Participants with Serious Adverse Events (SAEs)

End point description:

An SAE is defined as any untoward medical occurrence or effect that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability / incapacity, is a congenital anomaly / birth defect or is medically important which may require intervention to prevent the items listed above or may expose the participant to danger. Safety Set included all randomized participants who received at least 1 dose of IPs.

End point type	Secondary

End point timeframe:

From first vaccination (Day 1 [Month 0]) through end of study (Day 360 [Month 12])

End point values	9vHPV+TDV	9vHPV		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	307	307		
Units: percentage of participants				
number (not applicable)	10.1	7.2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality and serious adverse events: From first vaccination (Day 1 [Month 0]) through end of study (Day 360 [Month 12]); Non-serious adverse events: Unsolicited adverse events: Up to 28 days (day of vaccination + 27 days) after each vaccination

Adverse event reporting additional description:

Safety Set included all randomized participants who received at least 1 dose of IPs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26

Reporting groups

Reporting group title	9vHPV

Reporting group description:

Participants received 0.5 mL 9vHPV IM once on Day 1 (Month 0) followed by 0.5 mL 9vHPV IM once on Day 180 (Month 6).

Reporting group title	9vHPV+TDV

Reporting group description:

Participants received 0.5 mL 9vHPV IM and 0.5 mL TDV SC once on Day 1 (Month 0) followed by 0.5 mL TDV SC once on Day 90 (Month 3) and 0.5 mL 9vHPV IM once on Day 180 (Month 6).

Serious adverse events	9vHPV	9vHPV+TDV	
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 307 (7.17%)	31 / 307 (10.10%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Foreign body in gastrointestinal tract			
subjects affected / exposed	0 / 307 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Limb injury			
subjects affected / exposed	1 / 307 (0.33%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			

subjects affected / exposed	1 / 307 (0.33%)	0 / 307 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 307 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 307 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19			
subjects affected / exposed	19 / 307 (6.19%)	26 / 307 (8.47%)	
occurrences causally related to treatment / all	0 / 19	0 / 26	
deaths causally related to treatment / all	0 / 0	0 / 0	
COVID-19 pneumonia			
subjects affected / exposed	2 / 307 (0.65%)	2 / 307 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	0 / 307 (0.00%)	1 / 307 (0.33%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	9vHPV	9vHPV+TDV	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	223 / 307 (72.64%)	253 / 307 (82.41%)	
Injury, poisoning and procedural complications			

Wound			
subjects affected / exposed	0 / 307 (0.00%)	1 / 307 (0.33%)	
occurrences (all)	0	1	
Skin abrasion			
subjects affected / exposed	0 / 307 (0.00%)	1 / 307 (0.33%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	59 / 307 (19.22%)	71 / 307 (23.13%)	
occurrences (all)	93	207	
Syncope			
subjects affected / exposed	0 / 307 (0.00%)	1 / 307 (0.33%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	1 / 307 (0.33%)	8 / 307 (2.61%)	
occurrences (all)	1	11	
Asthenia			
subjects affected / exposed	40 / 307 (13.03%)	58 / 307 (18.89%)	
occurrences (all)	79	159	
Malaise			
subjects affected / exposed	36 / 307 (11.73%)	62 / 307 (20.20%)	
occurrences (all)	61	153	
Injection site pain			
subjects affected / exposed	1 / 307 (0.33%)	0 / 307 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	0 / 307 (0.00%)	2 / 307 (0.65%)	
occurrences (all)	0	2	
Swelling			
subjects affected / exposed	52 / 307 (16.94%)	64 / 307 (20.85%)	
occurrences (all)	147	319	
Pain			
subjects affected / exposed	184 / 307 (59.93%)	225 / 307 (73.29%)	
occurrences (all)	359	983	
Blood and lymphatic system disorders			

Iron deficiency anaemia subjects affected / exposed occurrences (all)	0 / 307 (0.00%) 0	1 / 307 (0.33%) 1	
Eye disorders Conjunctivitis allergic subjects affected / exposed occurrences (all)	1 / 307 (0.33%) 1	0 / 307 (0.00%) 0	
Gastrointestinal disorders Flatulence subjects affected / exposed occurrences (all) Aphthous ulcer subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	 1 / 307 (0.33%) 1 0 / 307 (0.00%) 0 1 / 307 (0.33%) 1	 0 / 307 (0.00%) 0 1 / 307 (0.33%) 1 2 / 307 (0.65%) 2	
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all)	 0 / 307 (0.00%) 0	 1 / 307 (0.33%) 1	
Skin and subcutaneous tissue disorders Dermatitis contact subjects affected / exposed occurrences (all) Erythema subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Urticaria subjects affected / exposed occurrences (all)	 0 / 307 (0.00%) 0 57 / 307 (18.57%) 146 0 / 307 (0.00%) 0 1 / 307 (0.33%) 1	 2 / 307 (0.65%) 2 92 / 307 (29.97%) 501 1 / 307 (0.33%) 1 1 / 307 (0.33%) 1	
Musculoskeletal and connective tissue disorders			

Myalgia			
subjects affected / exposed	93 / 307 (30.29%)	135 / 307 (43.97%)	
occurrences (all)	181	475	
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	0 / 307 (0.00%)	2 / 307 (0.65%)	
occurrences (all)	0	2	
Nasopharyngitis			
subjects affected / exposed	0 / 307 (0.00%)	3 / 307 (0.98%)	
occurrences (all)	0	3	
Gastroenteritis			
subjects affected / exposed	0 / 307 (0.00%)	1 / 307 (0.33%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	0 / 307 (0.00%)	1 / 307 (0.33%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 March 2021	The following changes were implemented as per Amendment 2: 1. Update in responsibilities of the signatory investigator. 2. Addition of trial risk management. 3. Administrative change of the details of the medical director and clinical project oversight manager. 4. Deletion of proprietary table showing lower limits of quantification and serostatus cut-offs for each of the 9 vaccine HPV types.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported