



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

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 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 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 occurrences (all) | 0 / 307 (0.00%) 0 | 1 / 307 (0.33%) 1 | |
| Skin abrasion subjects affected / exposed occurrences (all) | 0 / 307 (0.00%) 0 | 1 / 307 (0.33%) 1 | |
| Nervous system disorders | | | |
| Headache subjects affected / exposed occurrences (all) | 59 / 307 (19.22%) 93 | 71 / 307 (23.13%) 207 | |
| Syncope subjects affected / exposed occurrences (all) | 0 / 307 (0.00%) 0 | 1 / 307 (0.33%) 1 | |
| General disorders and administration site conditions | | | |
| Fever subjects affected / exposed occurrences (all) | 1 / 307 (0.33%) 1 | 8 / 307 (2.61%) 11 | |
| Asthenia subjects affected / exposed occurrences (all) | 40 / 307 (13.03%) 79 | 58 / 307 (18.89%) 159 | |
| Malaise subjects affected / exposed occurrences (all) | 36 / 307 (11.73%) 61 | 62 / 307 (20.20%) 153 | |
| Injection site pain subjects affected / exposed occurrences (all) | 1 / 307 (0.33%) 1 | 0 / 307 (0.00%) 0 | |
| Pyrexia subjects affected / exposed occurrences (all) | 0 / 307 (0.00%) 0 | 2 / 307 (0.65%) 2 | |
| Swelling subjects affected / exposed occurrences (all) | 52 / 307 (16.94%) 147 | 64 / 307 (20.85%) 319 | |
| Pain subjects affected / exposed occurrences (all) | 184 / 307 (59.93%) 359 | 225 / 307 (73.29%) 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 occurrences (all) | 93 / 307 (30.29%) 181 | 135 / 307 (43.97%) 475 | |
| Infections and infestations | | | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 0 / 307 (0.00%) 0 | 2 / 307 (0.65%) 2 | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 0 / 307 (0.00%) 0 | 3 / 307 (0.98%) 3 | |
| Gastroenteritis subjects affected / exposed occurrences (all) | 0 / 307 (0.00%) 0 | 1 / 307 (0.33%) 1 | |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia subjects affected / exposed occurrences (all) | 0 / 307 (0.00%) 0 | 1 / 307 (0.33%) 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