



Clinical trial results:

A Randomized, Observer Blind, Phase 3 Trial to Investigate the Immunogenicity and Safety of the Co-administration of a Subcutaneous Tetravalent Dengue Vaccine Candidate (TDV) and an Intramuscular Hepatitis A Virus (Inactivated) Vaccine in Healthy Subjects Aged 18 to 60 Years in Non-endemic Country(ies) for Dengue

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2017-001071-23 |
| Trial protocol | GB |
| Global end of trial date | 25 July 2019 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 10 July 2020 |
| First version publication date | 10 July 2020 |

Trial information

Trial identification

| | |
|-----------------------|---------|
| Sponsor protocol code | DEN-314 |
|-----------------------|---------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Takeda |
| Sponsor organisation address | Takeda Vaccines, Inc., 40 Landsdowne Street, United States, Cambridge |
| Public contact | Medical Director, Takeda Vaccines, Inc., +1 8778253327, trialdisclosures@takeda.com |
| Scientific contact | Medical Director, Takeda, +1 8778253327, 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? | No |

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 16 May 2016 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 25 July 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study is to investigate the immunogenicity and safety of the concomitant administration of TDV (subcutaneous [SC] injection) and of hepatitis A virus (HAV) vaccine (intramuscular [IM] injection) in healthy participants aged 18 to 60 years living in country(ies) non-endemic for both dengue and hepatitis.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------|
| Actual start date of recruitment | 16 May 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|---------------------|
| Country: Number of subjects enrolled | United Kingdom: 900 |
| Worldwide total number of subjects | 900 |
| EEA total number of subjects | 900 |

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) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 900 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 10 investigative sites in United Kingdom from 16-May-2018 to 09-Jul-2019.

Pre-assignment

Screening details:

Healthy participants were randomized in 1:1:1 ratio in 3 parallel groups: Group 1 received 1 dose of Hepatitis A Virus (HAV) vaccine and Tetravalent Dengue Vaccine Candidate (TDV) placebo matching injection, Group 2 received 2 doses of TDV and HAV vaccine placebo matching injection and Group 3 received 1 dose of HAV vaccine and 2 doses of TDV.

Period 1

| | |
|------------------------------|--|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator, Monitor, Data analyst, Assessor |

Arms

| | |
|------------------------------|---------------------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | HAV Vaccine 1.0 ml + Placebo/ Placebo |

Arm description:

HAV vaccine 1.0 ml, injection, intramuscular (IM), and TDV placebo-matching injection, subcutaneous (SC), once on Day 1 (first dose) followed by TDV placebo-matching injection, SC on Day 90 (second dose).

| | |
|--|------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Normal saline (0.9% NaCl) subcutaneous (SC) injection, once on Day 1 and 90.

| | |
|--|--------------------|
| Investigational medicinal product name | HAV Vaccine 1.0 ml |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

HAV vaccine intramuscular (IM) injection, once on Day 1

| | |
|------------------|----------------------------------|
| Arm title | TDV 0.5 ml + Placebo/ TDV 0.5 ml |
|------------------|----------------------------------|

Arm description:

TDV 0.5 ml, injection, SC, and HAV vaccine placebo-matching injection, IM, once on Day 1 (first dose) followed by TDV 0.5 ml, injection, SC on Day 90 (second dose).

| | |
|--|-------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |

| | |
|---|--|
| Dosage and administration details: | |
| Normal saline (0.9% NaCl) IM injection, once on Day 1 | |
| Investigational medicinal product name | Takeda's tetravalent dengue vaccine candidate (TDV) 0.5 ml |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: | |
| TDV 0.5 ml SC, once on Day 1 and 90. | |
| Arm title | TDV 0.5 ml + HAV Vaccine 1.0 ml/ TDV 0.5 ml |
| Arm description: | |
| TDV 0.5 ml, injection, SC, and HAV vaccine 1.0 ml, injection, IM, once on Day 1 (first dose) followed by TDV 0.5 ml, injection, SC on Day 90 (second dose). | |
| Arm type | Experimental |
| Investigational medicinal product name | HAV 1.0 ml vaccine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Intramuscular use |
| Dosage and administration details: | |
| HAV 1.0 ml, IM, once on Day 1. | |
| Investigational medicinal product name | TDV 0.5 ml |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Injection |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: | |
| TDV 0.5 ml, SC, once on Day 1 and 90 | |

| Number of subjects in period 1 | HAV Vaccine 1.0 ml + Placebo/ Placebo | TDV 0.5 ml + Placebo/ TDV 0.5 ml | TDV 0.5 ml + HAV Vaccine 1.0 ml/ TDV 0.5 ml |
|--------------------------------|--|-------------------------------------|---|
| | | | |
| Started | 300 | 300 | 300 |
| Safety Population | 299 | 300 | 298 |
| Completed | 261 | 261 | 259 |
| Not completed | 39 | 39 | 41 |
| Consent withdrawn by subject | 5 | 4 | 2 |
| Adverse event, non-fatal | - | 1 | - |
| Lost to follow-up | 32 | 33 | 37 |
| Reason not Specified | 2 | 1 | 2 |

Baseline characteristics

Reporting groups

| | |
|--|---|
| Reporting group title | HAV Vaccine 1.0 ml + Placebo/ Placebo |
| Reporting group description: HAV vaccine 1.0 ml, injection, intramuscular (IM), and TDV placebo-matching injection, subcutaneous (SC), once on Day 1 (first dose) followed by TDV placebo-matching injection, SC on Day 90 (second dose). | |
| Reporting group title | TDV 0.5 ml + Placebo/ TDV 0.5 ml |
| Reporting group description: TDV 0.5 ml, injection, SC, and HAV vaccine placebo-matching injection, IM, once on Day 1 (first dose) followed by TDV 0.5 ml, injection, SC on Day 90 (second dose). | |
| Reporting group title | TDV 0.5 ml + HAV Vaccine 1.0 ml/ TDV 0.5 ml |
| Reporting group description: TDV 0.5 ml, injection, SC, and HAV vaccine 1.0 ml, injection, IM, once on Day 1 (first dose) followed by TDV 0.5 ml, injection, SC on Day 90 (second dose). | |

| Reporting group values | HAV Vaccine 1.0 ml + Placebo/ Placebo | TDV 0.5 ml + Placebo/ TDV 0.5 ml | TDV 0.5 ml + HAV Vaccine 1.0 ml/ TDV 0.5 ml |
|---|---------------------------------------|----------------------------------|---|
| Number of subjects | 300 | 300 | 300 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 300 | 300 | 300 |
| Age Continuous Units: years | | | |
| arithmetic mean | 34.7 | 36.0 | 35.5 |
| standard deviation | ± 12.03 | ± 11.88 | ± 11.94 |
| Sex: Female, Male Units: participants | | | |
| Female | 107 | 120 | 90 |
| Male | 193 | 180 | 210 |
| Ethnicity (NIH/OMB) Units: Subjects | | | |
| Hispanic or Latino | 6 | 4 | 1 |
| Not Hispanic or Latino | 290 | 293 | 296 |
| Unknown or Not Reported | 4 | 3 | 3 |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 1 | 0 | 0 |
| Asian | 5 | 9 | 11 |
| Native Hawaiian or Other Pacific Islander | 1 | 1 | 0 |
| Black or African American | 6 | 4 | 6 |
| White | 280 | 281 | 279 |
| More than one race | 7 | 4 | 4 |
| Unknown or Not Reported | 0 | 1 | 0 |
| Height Units: cm | | | |
| arithmetic mean | | 172.12 | |
| standard deviation | ± | ± 9.163 | ± |

| | | | |
|--------------------------|---|----------|---|
| Weight | | | |
| Units: kg | | | |
| arithmetic mean | | 78.18 | |
| standard deviation | ± | ± 15.570 | ± |
| Body Mass Index (BMI) | | | |
| BMI=Weight/Height. | | | |
| Units: kg/m ² | | | |
| arithmetic mean | | 26.31 | |
| standard deviation | ± | ± 4.354 | ± |

| | | | |
|---|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 900 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 900 | | |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Sex: Female, Male | | | |
| Units: participants | | | |
| Female | 317 | | |
| Male | 583 | | |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 11 | | |
| Not Hispanic or Latino | 879 | | |
| Unknown or Not Reported | 10 | | |
| Race (NIH/OMB) | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 1 | | |
| Asian | 25 | | |
| Native Hawaiian or Other Pacific Islander | 2 | | |
| Black or African American | 16 | | |
| White | 840 | | |
| More than one race | 15 | | |
| Unknown or Not Reported | 1 | | |
| Height | | | |
| Units: cm | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Weight | | | |
| Units: kg | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Body Mass Index (BMI) | | | |
| BMI=Weight/Height. | | | |
| Units: kg/m ² | | | |
| arithmetic mean | | | |
| standard deviation | - | | |

Subject analysis sets

| | |
|--|---|
| Subject analysis set title | HAV Vaccine 1.0 ml + Placebo/ Placebo |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: HAV vaccine 1.0 ml, injection, IM, and TDV placebo-matching injection, SC, once on Day 1 (first dose) followed by TDV placebo-matching injection, SC on Day 90 (second dose). | |
| Subject analysis set title | TDV 0.5 ml + HAV Vaccine 1.0 ml/ TDV 0.5 ml |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: TDV 0.5 ml, injection, SC, and HAV vaccine 1.0 ml, injection, IM, once on Day 1 (first dose) followed by TDV 0.5 ml, injection, SC on Day 90 (second dose). | |
| Subject analysis set title | HAV Vaccine 1.0 ml + Placebo/ Placebo |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: HAV vaccine 1.0 ml, injection, IM, and TDV placebo-matching injection, SC, once on Day 1 (first dose) followed by TDV placebo-matching injection, SC on Day 90 (second dose). | |
| Subject analysis set title | TDV 0.5 ml + Placebo/ TDV 0.5 ml |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: TDV 0.5 ml, injection, SC, and HAV vaccine placebo-matching injection, IM, once on Day 1 (first dose) followed by TDV 0.5 ml, injection, SC on Day 90 (second dose). | |
| Subject analysis set title | TDV 0.5 ml + HAV Vaccine 1.0 ml/ TDV 0.5 ml |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: TDV 0.5 ml, injection, SC, and HAV vaccine 1.0 ml, injection, IM, once on Day 1 (first dose) followed by TDV 0.5 ml, injection, SC on Day 90 (second dose). | |
| Subject analysis set title | TDV 0.5 ml + Placebo/ TDV 0.5 ml |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: TDV 0.5 ml, injection, SC, and placebo-matching injection, IM, once on Day 1 (first dose) followed by TDV 0.5 ml, injection, SC on Day 90 (second dose). | |
| Subject analysis set title | TDV 0.5 ml + HAV Vaccine 1.0 ml/ TDV 0.5 ml |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: TDV 0.5 ml, injection, SC, and HAV vaccine 1.0 ml, injection, IM, once on Day 1 (first dose) followed by TDV 0.5 ml, injection, SC on Day 90 (second dose). | |

| Reporting group values | HAV Vaccine 1.0 ml + Placebo/ Placebo | TDV 0.5 ml + HAV Vaccine 1.0 ml/ TDV 0.5 ml | HAV Vaccine 1.0 ml + Placebo/ Placebo |
|---|---------------------------------------|---|---------------------------------------|
| Number of subjects | 299 | 297 | 118 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | | | |
| Age Continuous Units: years arithmetic mean standard deviation | ± | ± | ± |
| Sex: Female, Male Units: participants | | | |
| 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 | | | |
| Height Units: cm arithmetic mean standard deviation | 173.80 ± 9.299 | 173.00 ± 9.110 | ± |
| Weight Units: kg arithmetic mean standard deviation | 79.24 ± 15.547 | 78.92 ± 15.243 | ± |
| Body Mass Index (BMI) | | | |
| BMI=Weight/Height. Units: kg/m ² | | | |
| arithmetic mean standard deviation | 26.16 ± 4.256 | 26.29 ± 4.283 | ± |

| Reporting group values | TDV 0.5 ml + Placebo/ TDV 0.5 ml | TDV 0.5 ml + HAV Vaccine 1.0 ml/ TDV 0.5 ml | TDV 0.5 ml + Placebo/ TDV 0.5 ml |
|---|-------------------------------------|---|-------------------------------------|
| Number of subjects | 121 | 122 | 119 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | | | |
| Age Continuous Units: years arithmetic mean standard deviation | ± | ± | ± |
| Sex: Female, Male Units: participants | | | |
| 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 | | | |
| Height Units: cm arithmetic mean standard deviation | ± | ± | ± |
| Weight Units: kg arithmetic mean standard deviation | ± | ± | ± |
| Body Mass Index (BMI) | | | |
| BMI=Weight/Height. Units: kg/m ² arithmetic mean standard deviation | | | |
| | ± | ± | ± |

| | | | |
|---|---|--|--|
| Reporting group values | TDV 0.5 ml + HAV Vaccine 1.0 ml/ TDV 0.5 ml | | |
| Number of subjects | 120 | | |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | | | |
| Age Continuous Units: years arithmetic mean standard deviation | ± | | |
| Sex: Female, Male Units: participants | | | |
| 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 | | | |

| | | | |
|---|-------|--|--|
| Height Units: cm arithmetic mean standard deviation | \pm | | |
| Weight Units: kg arithmetic mean standard deviation | \pm | | |
| Body Mass Index (BMI) | | | |
| BMI=Weight/Height. | | | |
| Units: kg/m ² arithmetic mean standard deviation | \pm | | |

End points

End points reporting groups

| | |
|--|---|
| Reporting group title | HAV Vaccine 1.0 ml + Placebo/ Placebo |
| Reporting group description: HAV vaccine 1.0 ml, injection, intramuscular (IM), and TDV placebo-matching injection, subcutaneous (SC), once on Day 1 (first dose) followed by TDV placebo-matching injection, SC on Day 90 (second dose). | |
| Reporting group title | TDV 0.5 ml + Placebo/ TDV 0.5 ml |
| Reporting group description: TDV 0.5 ml, injection, SC, and HAV vaccine placebo-matching injection, IM, once on Day 1 (first dose) followed by TDV 0.5 ml, injection, SC on Day 90 (second dose). | |
| Reporting group title | TDV 0.5 ml + HAV Vaccine 1.0 ml/ TDV 0.5 ml |
| Reporting group description: TDV 0.5 ml, injection, SC, and HAV vaccine 1.0 ml, injection, IM, once on Day 1 (first dose) followed by TDV 0.5 ml, injection, SC on Day 90 (second dose). | |
| Subject analysis set title | HAV Vaccine 1.0 ml + Placebo/ Placebo |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: HAV vaccine 1.0 ml, injection, IM, and TDV placebo-matching injection, SC, once on Day 1 (first dose) followed by TDV placebo-matching injection, SC on Day 90 (second dose). | |
| Subject analysis set title | TDV 0.5 ml + HAV Vaccine 1.0 ml/ TDV 0.5 ml |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: TDV 0.5 ml, injection, SC, and HAV vaccine 1.0 ml, injection, IM, once on Day 1 (first dose) followed by TDV 0.5 ml, injection, SC on Day 90 (second dose). | |
| Subject analysis set title | HAV Vaccine 1.0 ml + Placebo/ Placebo |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: HAV vaccine 1.0 ml, injection, IM, and TDV placebo-matching injection, SC, once on Day 1 (first dose) followed by TDV placebo-matching injection, SC on Day 90 (second dose). | |
| Subject analysis set title | TDV 0.5 ml + Placebo/ TDV 0.5 ml |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: TDV 0.5 ml, injection, SC, and HAV vaccine placebo-matching injection, IM, once on Day 1 (first dose) followed by TDV 0.5 ml, injection, SC on Day 90 (second dose). | |
| Subject analysis set title | TDV 0.5 ml + HAV Vaccine 1.0 ml/ TDV 0.5 ml |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: TDV 0.5 ml, injection, SC, and placebo-matching injection, IM, once on Day 1 (first dose) followed by TDV 0.5 ml, injection, SC on Day 90 (second dose). | |
| Subject analysis set title | TDV 0.5 ml + HAV Vaccine 1.0 ml/ TDV 0.5 ml |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: TDV 0.5 ml, injection, SC, and HAV vaccine 1.0 ml, injection, IM, once on Day 1 (first dose) followed by TDV 0.5 ml, injection, SC on Day 90 (second dose). | |
| Subject analysis set title | TDV 0.5 ml + Placebo/ TDV 0.5 ml |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: TDV 0.5 ml, injection, SC, and placebo-matching injection, IM, once on Day 1 (first dose) followed by TDV 0.5 ml, injection, SC on Day 90 (second dose). | |
| Subject analysis set title | TDV 0.5 ml + HAV Vaccine 1.0 ml/ TDV 0.5 ml |
| Subject analysis set type | Sub-group analysis |
| Subject analysis set description: TDV 0.5 ml, injection, SC, and HAV vaccine 1.0 ml, injection, IM, once on Day 1 (first dose) followed by TDV 0.5 ml, injection, SC on Day 90 (second dose). | |

Primary: Percentage of Participants HAV/Dengue Virus (DENV)-naïve at Baseline who are Seroprotected Against HAV at Day 30

| | |
|-----------------|--|
| End point title | Percentage of Participants HAV/Dengue Virus (DENV)-naïve at Baseline who are Seroprotected Against HAV at Day 30 |
|-----------------|--|

End point description:

Seroprotection is defined as serum anti-HAV antibody levels ≥ 12.5 mIU/mL, measured by enzyme-linked immunosorbent assay (ELISA). Immunological naivety to HAV/DENV is defined as anti-HAV antibody levels < 12.5 mIU/mL and reciprocal neutralizing titers for all 4 dengue serotypes < 10 . The 4 dengue virus serotypes were DENV-1, DENV-2, DENV-3 and DENV-4. HAV PPS: All HAV & DENV-naïve participants in the immunogenicity subset who received at least 1 dose of trial vaccine, with available Day 1 and Day 30 HAV immunogenicity measurements, and who have no major protocol violations.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

One month post first vaccination (Day 30)

| End point values | HAV Vaccine 1.0 ml + Placebo/ Placebo | TDV 0.5 ml + Placebo/ TDV 0.5 ml | TDV 0.5 ml + HAV Vaccine 1.0 ml/ TDV 0.5 ml | |
|-----------------------------------|---------------------------------------|----------------------------------|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 68 | 66 | 79 | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 97.1 (89.8 to 99.6) | 9.1 (3.4 to 18.7) | 98.7 (93.1 to 100.0) | |

Statistical analyses

| | |
|----------------------------|--|
| Statistical analysis title | HAV Seroprotected Participants (Naïve) at Day 30 |
|----------------------------|--|

Statistical analysis description:

As per predefined criteria in protocol the non-inferiority was established only between group 1 and group 3. Non-inferiority of HAV+TDV to HAV was established if the upper bound of the 95% CI was less than 10%.

| | |
|---|---|
| Comparison groups | HAV Vaccine 1.0 ml + Placebo/ Placebo v TDV 0.5 ml + HAV Vaccine 1.0 ml/ TDV 0.5 ml |
| Number of subjects included in analysis | 147 |
| Analysis specification | Pre-specified |
| Analysis type | non-inferiority |
| Parameter estimate | Seroprotection Rate Difference |
| Point estimate | -1.68 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.91 |
| upper limit | 4.28 |

Secondary: Geometric Mean Titers (GMTs) of Neutralizing Antibodies for Each of the 4 Dengue Serotypes at Day 30 and Day 120 in Participants HAV/DENV-naïve at Baseline

| | |
|---|---|
| End point title | Geometric Mean Titers (GMTs) of Neutralizing Antibodies for Each of the 4 Dengue Serotypes at Day 30 and Day 120 in Participants HAV/DENV-naïve at Baseline |
| End point description: GMTs of neutralizing antibodies were measured by microneutralization test 50% [MNT50] for each of the 4 Dengue Serotypes. The 4 dengue virus serotypes were DENV-1, DENV-2, DENV-3 and DENV-4. TDV PPS: All HAV & DENV-naïve participants in the immunogenicity subset who received at least 1 dose of trial vaccine, with available Day 1 and at least 1 post-dose immunogenicity measurements, and who have no major protocol violations. Number analyzed are participants with data available at the given timepoint. 99999: Lower and upper limits of CI could not be evaluated as titers were below the lower limit of detection (LLOD). | |
| End point type | Secondary |
| End point timeframe: One month post first vaccination (Day 30) and one month post second vaccination (Day 120) | |

| End point values | HAV Vaccine 1.0 ml + Placebo/ Placebo | TDV 0.5 ml + Placebo/ TDV 0.5 ml | TDV 0.5 ml + HAV Vaccine 1.0 ml/ TDV 0.5 ml | |
|--|---------------------------------------|----------------------------------|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 66 | 63 | 67 | |
| Units: titer | | | | |
| geometric mean (confidence interval 95%) | | | | |
| DENV 1, Day 30 (n=61,60,65) | 99999 (99999 to 99999) | 108.2 (69.2 to 169.1) | 152.5 (104.4 to 222.8) | |
| DENV 2, Day 30 (n=61,60,65) | 6.0 (5.1 to 7.1) | 2897.9 (1469.2 to 5715.6) | 3960.0 (2310.7 to 6786.5) | |
| DENV 3, Day 30 (n=61,60,65) | 5.3 (4.7 to 5.8) | 95.4 (59.5 to 153.2) | 140.5 (96.8 to 203.9) | |
| DENV 4, Day 30 (n=61,60,65) | 99999 (99999 to 99999) | 74.3 (49.0 to 112.9) | 142.1 (90.5 to 223.2) | |
| DENV 1, Day 120 (n=50,55,62) | 99999 (99999 to 99999) | 171.3 (104.5 to 281.0) | 173.7 (120.1 to 251.3) | |
| DENV 2, Day 120 (n=50,55,62) | 5.7 (4.9 to 6.7) | 2064.1 (1459.7 to 2918.9) | 1764.3 (1238.6 to 2513.0) | |
| DENV 3, Day 120 (n=50,55,62) | 99999 (99999 to 99999) | 83.8 (59.0 to 119.0) | 92.6 (71.3 to 120.3) | |
| DENV 4, Day 120 (n=50,55,62) | 99999 (99999 to 99999) | 56.1 (41.0 to 76.7) | 81.4 (59.2 to 111.8) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants HAV/DENV-naïve at Baseline who are Seropositive for Each of the 4 Dengue Serotypes at Day 30 and Day 120

| | |
|-----------------|---|
| End point title | Percentage of Participants HAV/DENV-naïve at Baseline who are Seropositive for Each of the 4 Dengue Serotypes at Day 30 and Day 120 |
|-----------------|---|

End point description:

Seropositivity is defined as a reciprocal neutralizing titer ≥ 10 . The 4 dengue virus serotypes were DENV-

1, DENV-2, DENV-3 and DENV-4. TDV PPS: All HAV & DENV-naïve participants in the immunogenicity subset who received at least 1 dose of trial vaccine, with available Day 1 and at least 1 post-dose immunogenicity measurements, and who have no major protocol violations. n=number analyzed are participants with data available at the given timepoint.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| One month post first vaccination (Day 30) and one month post second vaccination (Day 120) | |

| End point values | HAV Vaccine 1.0 ml + Placebo/ Placebo | TDV 0.5 ml + Placebo/ TDV 0.5 ml | TDV 0.5 ml + HAV Vaccine 1.0 ml/ TDV 0.5 ml | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 66 | 63 | 67 | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | | | | |
| DENV 1, Day 30 (n=61,60,65) | 0 (0.0 to 5.9) | 88.3 (77.4 to 95.2) | 95.4 (87.1 to 99.0) | |
| DENV 2, Day 30 (n=61,60,65) | 8.2 (2.7 to 18.1) | 91.7 (81.6 to 97.2) | 96.9 (89.3 to 99.6) | |
| DENV 3, Day 30 (n=61,60,65) | 1.6 (0.0 to 8.8) | 85.0 (73.4 to 92.9) | 95.4 (87.1 to 99.0) | |
| DENV 4, Day 30 (n=61,60,65) | 0 (0.0 to 5.9) | 86.7 (75.4 to 94.1) | 90.8 (81.0 to 96.5) | |
| DENV 1, Day 120 (n=50,55,62) | 0 (0.0 to 7.1) | 100.0 (93.5 to 100.0) | 100.0 (94.2 to 100.0) | |
| DENV 2, Day 120 (n=50,55,62) | 6.0 (1.3 to 16.5) | 100.0 (93.5 to 100.0) | 100.0 (94.2 to 100.0) | |
| DENV 3, Day 120 (n=50,55,62) | 0 (0.0 to 7.1) | 92.7 (82.4 to 98.0) | 98.4 (91.3 to 100.0) | |
| DENV 4, Day 120 (n=50,55,62) | 0 (0.0 to 7.1) | 96.4 (87.5 to 99.6) | 96.8 (88.8 to 99.6) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Geometric Mean Concentrations (GMC) of Anti-HAV Antibodies at Day 30 in Participants HAV/DENV-naïve at Baseline

| | |
|-----------------|---|
| End point title | Geometric Mean Concentrations (GMC) of Anti-HAV Antibodies at Day 30 in Participants HAV/DENV-naïve at Baseline |
|-----------------|---|

End point description:

GMC of anti-HAV antibodies were measured by ELISA. The 4 dengue virus serotypes were DENV-1, DENV-2, DENV-3 and DENV-4. HAV PPS: All HAV & DENV-naïve participants in the immunogenicity subset who received at least 1 dose of trial vaccine, with available Day 1 and Day 30 HAV immunogenicity measurements, and who have no major protocol violations.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| One month post first vaccination (Day 30) | |

| End point values | HAV Vaccine 1.0 ml + Placebo/ Placebo | TDV 0.5 ml + Placebo/ TDV 0.5 ml | TDV 0.5 ml + HAV Vaccine 1.0 ml/ TDV 0.5 ml | |
|---|--|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 68 | 66 | 79 | |
| Units: mIU/mL | | | | |
| geometric mean (confidence interval 95%) | 82.1 (62.9 to 107.1) | 6.7 (6.4 to 7.2) | 93.0 (76.1 to 113.6) | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Solicited (Local Injection) Site Adverse Events (AEs) by Severity After Each Vaccination

| | |
|-----------------|--|
| End point title | Percentage of Participants with Solicited (Local Injection) Site Adverse Events (AEs) by Severity After Each Vaccination |
|-----------------|--|

End point description:

Solicited local AEs (at injection site) were collected by participants using diary cards within 7 days after vaccination (Vacc.) and included pain (none, mild: no interference with daily activity, moderate: interference with daily activity with or without treatment and severe: prevents daily activity with or without treatment), redness (erythema) (<2.5 cm, mild: 2.5-5 cm, moderate: >5 to <=10 cm, severe: >10 cm) and swelling (edema/induration) (<2.5 cm, mild: 2.5-5 cm, moderate: >5 to <=10 cm, severe: >10 cm). The percentages were rounded off to the first decimal place. Safety Set included all participants who received at least 1 dose of trial vaccine. n=number analyzed is the number of participants with data available for the specific category. Only categories for which there was at least 1 participant are reported. First=1st, second=2nd and vaccination (Vac).

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Within 7 days after each vaccination

| End point values | HAV Vaccine 1.0 ml + Placebo/ Placebo | TDV 0.5 ml + Placebo/ TDV 0.5 ml | TDV 0.5 ml + HAV Vaccine 1.0 ml/ TDV 0.5 ml | |
|--|--|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 299 | 300 | 298 | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| After 1st Vac. IM,Any Local AEs(n=289,292,285) | 45.0 | 15.4 | 49.1 | |
| After 1st Vac., IM, Pain-Mild (n=289,292,285) | 38.1 | 13.0 | 43.9 | |
| After 1st Vac., IM, Pain- Moderate(n=289,292,285) | 6.6 | 1.0 | 4.2 | |
| After 1st Vac., IM, Pain-Severe (n=289,292,285) | 0 | 0.3 | 0.4 | |

| | | | | |
|--|------|------|------|--|
| After 1st Vac., IM, Erythema-Mild(n=287,291,285) | 1.7 | 1.4 | 1.1 | |
| After 1st Vac, IM,Erythema-Moderate(n=287,291,285) | 0 | 0.3 | 0 | |
| After 1st Vac., IM, Swelling-Mild (n=285,291,285) | 1.4 | 0 | 0.7 | |
| After 1st Vac,SC,Any Solicited AEs(n=289,292,285) | 15.6 | 47.3 | 47.0 | |
| After 1st Vac., SC, Pain-Mild (n=289,292,285) | 12.5 | 35.6 | 36.1 | |
| After 1st Vac., SC, Pain-Moderate (n=289,292,285) | 1.7 | 4.8 | 6.3 | |
| After 1st Vac., SC, Erythema-Mild (n=286,291,285) | 1.0 | 15.8 | 12.3 | |
| After 1st Vac,SC,Erythema-Moderate (n=286,291,285) | 0 | 1.0 | 1.8 | |
| After 1st Vac., SC, Swelling-Mild (n=286,291,285) | 0.7 | 2.7 | 2.5 | |
| After 2nd Vac,SC,Any Local AEs (n=255,262,251) | 11.0 | 37.9 | 41.0 | |
| After 2nd Vac., SC,Pain-Mild (n=255,262,251) | 10.2 | 30.9 | 33.9 | |
| After 2nd Vac,SC,Pain-Moderate (n=255,262,251) | 0.4 | 2.7 | 3.2 | |
| After 2nd Vac,SC,Pain-Severe (n=255,262,251) | 0 | 1.1 | 0.8 | |
| After 2nd Vac,SC,Erythema-Mild (n=254,263,250) | 0.4 | 12.2 | 10.0 | |
| After 2nd Vac,SC,Erythema-Moderate (n=254,263,250) | 0 | 0.8 | 1.2 | |
| After 2nd Vac,SC,Swelling-Mild (n=254,263,249) | 0.8 | 3.4 | 4.4 | |
| After 2nd Vac,SC,Swelling-Moderate (n=254,263,249) | 0 | 0.8 | 0 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Solicited Systemic Adverse Events (AEs) by Severity After Each Vaccination

| | |
|-----------------|--|
| End point title | Percentage of Participants with Solicited Systemic Adverse Events (AEs) by Severity After Each Vaccination |
|-----------------|--|

End point description:

Solicited systemic AEs include fever, headache, asthenia, malaise and myalgia that occurred within 14 days after each vaccination. Solicited systemic AEs (headache, asthenia, malaise and myalgia) will be graded from 0 to 3 by severity; where 0=None, 1=Mild: No interference with daily activity, 2=Moderate: Interference with daily activity, 3=Severe: Prevents daily activity; Fever is defined as greater than or equal to 38°C (100.4°F) regardless of method taken. Fever was excluded from the overall count as no severity grading was applied for it. The percentages were rounded off to the first decimal place. Safety Set included all participants who received at least 1 dose of trial vaccine. n= number analyzed is the number of participants with data available for the specific category. Only categories for which there was at least 1 participant are reported.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Within 14 days after each vaccination

| End point values | HAV Vaccine 1.0 ml + Placebo/ Placebo | TDV 0.5 ml + Placebo/ TDV 0.5 ml | TDV 0.5 ml + HAV Vaccine 1.0 ml/ TDV 0.5 ml | |
|---|--|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 299 | 300 | 298 | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| After 1st Vac, Any Systemic AEs (n=289,292,285) | 47.4 | 44.2 | 49.5 | |
| After 1st Vac, Headache-Mild (n=289,292,285) | 19.0 | 22.3 | 20.7 | |
| After 1st Vac, Headache-Moderate (n=289,292,285) | 8.7 | 8.2 | 8.8 | |
| After 1st Vac, Headache-Severe (n=289,292,285) | 1.0 | 2.1 | 1.8 | |
| After 1st Vac, Asthenia-Mild (n=289,292,285) | 12.8 | 9.2 | 16.1 | |
| After 1st Vac, Asthenia-Moderate (n=289,292,285) | 4.2 | 5.5 | 4.2 | |
| After 1st Vac, Asthenia-Severe (n=289,292,285) | 0 | 1.0 | 0.4 | |
| After 1st Vac, Malaise-Mild (n=289,292,285) | 11.4 | 13.7 | 14.0 | |
| After 1st Vac, Malaise-Moderate (n=289,292,285) | 5.2 | 5.8 | 7.0 | |
| After 1st Vac, Malaise-Severe (n=289,292,285) | 1.0 | 1.7 | 0.7 | |
| After 1st Vac, Myalgia-Mild (n=289,292,285) | 23.9 | 16.4 | 27.7 | |
| After 1st Vac, Myalgia-Moderate (n=289,292,285) | 5.2 | 6.2 | 5.6 | |
| After 1st Vac, Myalgia-Severe (n=289,292,285) | 0.3 | 0.3 | 0.4 | |
| After 1st Vac, Fever-38.0-<38.5 (n=289,292,284) | 1.4 | 2.1 | 0.7 | |
| After 1st Vac, Fever-38.5-<39.0 (n=289,292,284) | 0.3 | 0.7 | 0.4 | |
| After 1st Vac, Fever-39.0-<39.5 (n=289,292,284) | 0 | 0 | 0.4 | |
| After 1st Vac, Fever-≥41.0 (n=289,292,284) | 0 | 0 | 0.4 | |
| After 2nd Vac, Any Systemic AEs (n=254,262,251) | 18.9 | 22.1 | 22.3 | |
| After 2nd Vac, Headache-Mild (n=254,262,251) | 13.0 | 12.6 | 14.7 | |
| After 2nd Vac, Headache-Moderate (n=254,262,251) | 4.3 | 3.4 | 6.0 | |
| After 2nd Vac, Headache-Severe (n=254,262,251) | 0.4 | 1.1 | 1.6 | |
| After 2nd Vac, Asthenia-Mild (n=254,262,251) | 7.5 | 5.0 | 7.6 | |
| After 2nd Vac, Asthenia-Moderate (n=254,262,251) | 2.4 | 2.7 | 1.6 | |
| After 2nd Vac, Asthenia-Severe (n=254,262,251) | 0 | 0 | 2.0 | |

| | | | | |
|--|------|------|------|--|
| After 2nd Vac, Malaise-Mild (n=254,262,251) | 10.2 | 9.9 | 10.4 | |
| After 2nd Vac, Malaise-Moderate (n=254,262,251) | 3.1 | 3.8 | 3.6 | |
| After 2nd Vac, Malaise-Severe (n=254,262,251) | 1.2 | 1.1 | 2.4 | |
| After 2nd Vac, Myalgia-Mild (n=254,262,251) | 10.2 | 13.0 | 15.9 | |
| After 2nd Vac, Myalgia-Moderate (n=254,262,251) | 2.0 | 1.9 | 3.2 | |
| After 2nd Vac, Myalgia-Severe (n=254,262,251) | 0.4 | 0.8 | 0.4 | |
| After 2nd Vac, Fever-38.0-<38.5 (n=251,262,250) | 3.2 | 0.4 | 0.8 | |
| After 2nd Vac, Fever-38.5-<39.0 (n=251,262,250) | 0 | 0.4 | 0 | |
| After 2nd Vac, Fever-39.5-<40.0 (n=251,262,250) | 0.4 | 0.4 | 0 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with any Unsolicited Adverse Events (AEs) After Each vaccination

| | |
|-----------------|---|
| End point title | Percentage of Participants with any Unsolicited Adverse Events (AEs) After Each vaccination |
|-----------------|---|

End point description:

An AE is defined as any untoward medical occurrence in a clinical investigation participant administered a trial vaccine; it does not necessarily have to have a causal relationship with trial vaccine administration. Safety Set included all participants who received at least 1 dose of trial vaccine. n=number analyzed is the number of participants with data available for the specific category.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Up to 28 days (Day of Vaccination+27 Subsequent Days) after each vaccination

| End point values | HAV Vaccine 1.0 ml + Placebo/ Placebo | TDV 0.5 ml + Placebo/ TDV 0.5 ml | TDV 0.5 ml + HAV Vaccine 1.0 ml/ TDV 0.5 ml | |
|---------------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 299 | 300 | 298 | |
| Units: percentage of participants | | | | |
| number (not applicable) | | | | |
| After 1st Vaccination (n=299,300,298) | 14.7 | 17.0 | 18.8 | |
| After 2nd Vaccination (n=270,271,257) | 14.4 | 10.0 | 11.7 | |

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:

A SAE is defined as any untoward medical occurrence that: 1) results in death, 2) is life-threatening, 3) requires inpatient hospitalization or prolongation of existing hospitalization, 4) results in persistent or significant disability/incapacity, 5) leads to a congenital anomaly/birth defect in the offspring of the participant or 6) is an medically important event that satisfies any of the following: a) May require intervention to prevent items 1 through 5 above. b) May expose the participant to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization. Safety Set included all participants who received at least 1 dose of trial vaccine.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From the first vaccination on Day 1 until the end of the trial (Day 270)

| End point values | HAV Vaccine 1.0 ml + Placebo/ Placebo | TDV 0.5 ml + Placebo/ TDV 0.5 ml | TDV 0.5 ml + HAV Vaccine 1.0 ml/ TDV 0.5 ml | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 299 | 300 | 298 | |
| Units: percentage of participants | | | | |
| number (not applicable) | 0.7 | 2.7 | 2.3 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with Medically Attended AEs (MAAEs)

| | |
|-----------------|--|
| End point title | Percentage of Participants with Medically Attended AEs (MAAEs) |
|-----------------|--|

End point description:

MAAEs are defined as AEs leading to a medical visit to or by a healthcare professional, including visits to an emergency department, but not fulfilling seriousness criteria. Safety Set included all participants who received at least 1 dose of trial vaccine.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From the first vaccination on Day 1 until the end of the trial (Day 270)

| End point values | HAV Vaccine 1.0 ml + Placebo/ Placebo | TDV 0.5 ml + Placebo/ TDV 0.5 ml | TDV 0.5 ml + HAV Vaccine 1.0 ml/ TDV 0.5 ml | |
|-----------------------------------|--|--|--|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 299 | 300 | 298 | |
| Units: percentage of participants | | | | |

| | | | | |
|-------------------------|------|------|------|--|
| number (not applicable) | 23.1 | 21.0 | 20.1 | |
|-------------------------|------|------|------|--|

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 the first vaccination on Day 1 until the end of the trial (Day 270); Other adverse events: Up to 28 days (Day of vaccination+27 subsequent days) after each vaccination.

Adverse event reporting additional description:

At each visit the investigator had to document any occurrence of adverse events and abnormal laboratory findings. Any event spontaneously reported by the participant or observed by the investigator was recorded, irrespective of the relation to study treatment.

| | |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 21.0 |

Reporting groups

| | |
|-----------------------|------------------------------|
| Reporting group title | HAV Vaccine 1.0 ml + Placebo |
|-----------------------|------------------------------|

Reporting group description:

Hepatitis A Virus (HAV) vaccine 1.0 ml, injection, intramuscular (IM), and placebo, injection, subcutaneous (SC), once on Day 1 (first dose) followed by placebo, injection, SC on Day 90 (second dose).

| | |
|-----------------------|----------------------|
| Reporting group title | TDV 0.5 ml + Placebo |
|-----------------------|----------------------|

Reporting group description:

Tetavalent Dengue Vaccine Candidate (TDV) 0.5 ml, injection, SC, and placebo, injection, IM, once on Day 1 (first dose) followed by TDV 0.5 ml, injection, SC on Day 90 (second dose).

| | |
|-----------------------|---------------------------------|
| Reporting group title | TDV 0.5 ml + HAV Vaccine 1.0 ml |
|-----------------------|---------------------------------|

Reporting group description:

TDV 0.5 ml, injection, SC, and HAV vaccine 1.0 ml, injection, IM, once on Day 1 (first dose) followed by TDV 0.5 ml, injection, SC on Day 90 (second dose).

| Serious adverse events | HAV Vaccine 1.0 ml + Placebo | TDV 0.5 ml + Placebo | TDV 0.5 ml + HAV Vaccine 1.0 ml |
|---|------------------------------|----------------------|---------------------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 299 (0.67%) | 8 / 300 (2.67%) | 7 / 298 (2.35%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Bladder cancer stage II | | | |
| subjects affected / exposed | 0 / 299 (0.00%) | 1 / 300 (0.33%) | 0 / 298 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Invasive ductal breast carcinoma | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 299 (0.00%) | 1 / 300 (0.33%) | 0 / 298 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 299 (0.00%) | 0 / 300 (0.00%) | 1 / 298 (0.34%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| Abdominal injury | | | |
| subjects affected / exposed | 0 / 299 (0.00%) | 1 / 300 (0.33%) | 0 / 298 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cervical vertebral fracture | | | |
| subjects affected / exposed | 0 / 299 (0.00%) | 0 / 300 (0.00%) | 1 / 298 (0.34%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fractured coccyx | | | |
| subjects affected / exposed | 1 / 299 (0.33%) | 0 / 300 (0.00%) | 0 / 298 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intentional overdose | | | |
| subjects affected / exposed | 0 / 299 (0.00%) | 0 / 300 (0.00%) | 1 / 298 (0.34%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Joint dislocation | | | |
| subjects affected / exposed | 0 / 299 (0.00%) | 1 / 300 (0.33%) | 0 / 298 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower limb fracture | | | |
| subjects affected / exposed | 0 / 299 (0.00%) | 0 / 300 (0.00%) | 1 / 298 (0.34%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thermal burn | | | |

| | | | |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 299 (0.00%) | 1 / 300 (0.33%) | 0 / 298 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 0 / 299 (0.00%) | 0 / 300 (0.00%) | 1 / 298 (0.34%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Loss of consciousness | | | |
| subjects affected / exposed | 0 / 299 (0.00%) | 1 / 300 (0.33%) | 0 / 298 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 299 (0.00%) | 1 / 300 (0.33%) | 0 / 298 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Abdominal strangulated hernia | | | |
| subjects affected / exposed | 1 / 299 (0.33%) | 0 / 300 (0.00%) | 0 / 298 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Crohn's disease | | | |
| subjects affected / exposed | 0 / 299 (0.00%) | 1 / 300 (0.33%) | 0 / 298 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intestinal ischaemia | | | |
| subjects affected / exposed | 0 / 299 (0.00%) | 0 / 300 (0.00%) | 1 / 298 (0.34%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Mesenteric vein thrombosis | | | |
| subjects affected / exposed | 0 / 299 (0.00%) | 0 / 300 (0.00%) | 1 / 298 (0.34%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|-----------------|-----------------|-----------------|
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 299 (0.00%) | 1 / 300 (0.33%) | 0 / 298 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute respiratory distress syndrome | | | |
| subjects affected / exposed | 0 / 299 (0.00%) | 0 / 300 (0.00%) | 1 / 298 (0.34%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Intentional self-injury | | | |
| subjects affected / exposed | 0 / 299 (0.00%) | 0 / 300 (0.00%) | 1 / 298 (0.34%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 0 / 299 (0.00%) | 1 / 300 (0.33%) | 0 / 298 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Wound infection | | | |
| subjects affected / exposed | 1 / 299 (0.33%) | 0 / 300 (0.00%) | 0 / 298 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

Frequency threshold for reporting non-serious adverse events: 2 %

| Non-serious adverse events | HAV Vaccine 1.0 ml + Placebo | TDV 0.5 ml + Placebo | TDV 0.5 ml + HAV Vaccine 1.0 ml |
|---|------------------------------|----------------------|---------------------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 9 / 299 (3.01%) | 8 / 300 (2.67%) | 11 / 298 (3.69%) |
| Infections and infestations | | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 9 / 299 (3.01%) | 8 / 300 (2.67%) | 11 / 298 (3.69%) |
| occurrences (all) | 11 | 8 | 11 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 27 December 2017 | Amendment 1: •The pregnancy test performed at screening was changed from a urine pregnancy test to a serum pregnancy test. Thereafter, urine pregnancy testing was considered acceptable provided that serum pregnancy testing was undertaken if the results were in doubt •The following phrase: "Other contraceptive methods may be considered in agreement with the Sponsor and was approved by the appropriate ethics committee" was rephrased to "Other contraceptive methods may be considered in agreement with the Sponsor and implemented only after approval of a substantial amendment by the regulatory authorities and by the appropriate ethics committee". |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported