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	±		
Weight Units: kg arithmetic mean standard deviation	±		
Body Mass Index (BMI)			
BMI=Weight/Height.			
Units: kg/m^2 arithmetic mean standard deviation	±		

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 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)-naive at Baseline who are Seroprotected Against HAV at Day 30

End point title	Percentage of Participants HAV/Dengue Virus (DENV)-naive 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-naive 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-naive 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-naive 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-naive 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-naive at Baseline

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

Tetravalent 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