Clinical trial results:
Phase III, Double-Blind, Randomized, Placebo-Controlled Trial to Investigate the Efficacy, Safety and Immunogenicity of a Tetravalent Dengue Vaccine (TDV) Administered Subcutaneously in Healthy Children Aged 4 - 16 Years Old

Summary

EudraCT number	2018-003979-34
Trial protocol	Outside EU/EEA
Global end of trial date	

Results information

Result version number	v1
This version publication date	12 March 2023
First version publication date	12 March 2023

Trial information

Trial identification

Sponsor protocol code	DEN-301

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02747927
WHO universal trial number (UTN)	U1111-1166-8401
Other trial identifiers	PHRR: PHRR150522-001010

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

Analysis stage	Interim
Date of interim/final analysis	11 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	11 July 2018
Global end of trial reached?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study is to evaluate the efficacy of 2 doses of Tetravalent Dengue Vaccine (TDV) in preventing symptomatic dengue fever of any severity and due to any of the four dengue virus serotypes in 4 to 16 year old participants.

Protection of trial subjects:

All study participants were required to read and sign an informed consent form. Assent was also obtained from the participant where required.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 September 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	Brazil: 1774
Country: Number of subjects enrolled	Colombia: 3900
Country: Number of subjects enrolled	Dominican Republic: 1600
Country: Number of subjects enrolled	Nicaragua: 825
Country: Number of subjects enrolled	Panama: 3000
Country: Number of subjects enrolled	Philippines: 3927
Country: Number of subjects enrolled	Sri Lanka: 2100
Country: Number of subjects enrolled	Thailand: 2973
Worldwide total number of subjects	20099
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	13661

Adolescents (12-17 years)	6438
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in the study at 26 investigative sites in the Philippines, Sri Lanka, Thailand, Brazil, Colombia, Dominican Republic, Nicaragua, Panama from 07 September 2016 to data cut-off date: 11 July 2018. The study is ongoing.

Pre-assignment

Screening details:

Healthy children received TDV or placebo (2:1 randomisation) in this study. The study was conducted in different Parts. Data is reported only up to Part 1 and primary outcome measure analysis up to 11 July 2018.

Pre-assignment period milestones

Number of subjects started	20099
Number of subjects completed	20067

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Did Not Receive Even 1 Dose of Trial Vaccine: 32

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, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo (Part 1)

Arm description:

Placebo-matching TDV, 0.5mL, subcutaneous (SC) injection on Day 1 (Month 0) and Day 90 (Month 3) in Part 1 of the study.

Arm type	Experimental
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

TDV placebo-matching SC injection.

Arm title	Tetravalent Dengue Vaccine (TDV) 0.5 mL (Part 1)

Arm description:

TDV, 0.5mL, subcutaneous (SC) injection on Day 1 (Month 0) and Day 90 (Month 3) in Part 1 of the study.

Arm type	Experimental
Investigational medicinal product name	Tetravalent Dengue Vaccine (TDV)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

TDV SC injection.

Number of subjects in period 1[1]	Placebo (Part 1)	Tetravalent Dengue Vaccine (TDV) 0.5 mL (Part 1)
Started	6687	13380
Completed	6476	12941
Not completed	211	439
Adverse event, non-fatal	5	14
Withdrawal by Subject and/or Parent/Guardian	138	289
Pregnancy	34	66
Lost to follow-up	22	43
Reason not Specified	10	24
Protocol deviation	2	3

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Only participants in the full analysis set who received at least 1 dose of the trial vaccines were included in the baseline period.

Baseline characteristics

Reporting groups	
Reporting group title	Placebo (Part 1)
Reporting group description:	
Placebo-matching TDV, 0.5mL, subcutaneous (SC) injection on Day 1 (Month 0) and Day 90 (Month 3) in Part 1 of the study.	
Reporting group title	Tetravalent Dengue Vaccine (TDV) 0.5 mL (Part 1)
Reporting group description:	
TDV, 0.5mL, subcutaneous (SC) injection on Day 1 (Month 0) and Day 90 (Month 3) in Part 1 of the study.	

Reporting group values	Placebo (Part 1)	Tetravalent Dengue Vaccine (TDV) 0.5 mL (Part 1)	Total
Number of subjects	6687	13380	20067
Age Categorical			
Units: Subjects			
Age continuous			
Units: years			
arithmetic mean	9.6	9.6	
standard deviation	± 3.34	± 3.36	-
Gender categorical			
Units: Subjects			
Male	3411	6729	10140
Female	3276	6651	9927
Race			
Units: Subjects			
American Indian or Alaska Native	2621	5234	7855
Asian	2985	5988	8973
Black or African American	758	1451	2209
Native Hawaiian or Other Pacific Islander	1	2	3
White	149	329	478
More than one race or Unknown	173	376	549
Height			
Units: cm			
arithmetic mean	135.00	134.95	
standard deviation	± 19.027	± 19.174	-
Weight			
Units: kg			
arithmetic mean	33.86	34.05	
standard deviation	± 14.540	± 14.976	-
Body Mass Index (BMI)			
BMI=weight (kg)/[height (m)^2]			
Units: kg/m^2			
arithmetic mean	17.68	17.78	
standard deviation	± 3.643	± 3.834	-

End points

End points reporting groups

Reporting group title	Placebo (Part 1)
Reporting group description:	
Placebo-matching TDV, 0.5mL, subcutaneous (SC) injection on Day 1 (Month 0) and Day 90 (Month 3) in Part 1 of the study.	
Reporting group title	Tetravalent Dengue Vaccine (TDV) 0.5 mL (Part 1)
Reporting group description:	
TDV, 0.5mL, subcutaneous (SC) injection on Day 1 (Month 0) and Day 90 (Month 3) in Part 1 of the study.	

Primary: Vaccine Efficacy (VE) of Two Doses of Tetravalent Dengue Vaccine (TDV) in Preventing Virologically-Confirmed Dengue Fever Induced by Any Dengue Serotype

End point title	Vaccine Efficacy (VE) of Two Doses of Tetravalent Dengue Vaccine (TDV) in Preventing Virologically-Confirmed Dengue Fever Induced by Any Dengue Serotype
End point description:	
The Vaccine Efficacy is defined as 1 - (λv/λc), where λv and λc denote the hazard rates for the TDV and placebo arms, respectively. A virologically-confirmed dengue case is defined as febrile illness (defined as temperature ≥38°C on any 2 of 3 consecutive days) or illness clinically suspected to be dengue by the Investigator with a positive serotype-specific reverse transcriptase polymerase chain reaction (RT-PCR). The primary endpoint of vaccine efficacy was assessed using the number of confirmed dengue cases that occurred during Part 1. Per protocol Set included include all participants in the Full analysis set (FAS) who have no major protocol violations. FAS included all randomised participants who received at least 1 dose of the trial vaccines.	
End point type	Primary
End point timeframe:	
30 days post-second vaccination (Day 120) until the end of Part 1 (Part 1 completed after 120 cases of confirmed dengue fever and minimum duration of participant follow-up of 12 months post-second vaccination)	

End point values	Placebo (Part 1)	Tetravalent Dengue Vaccine (TDV) 0.5 mL (Part 1)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6317	12704		
Units: number of cases	149	61		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Assuming true VE of 60% and, virologically confirmed cases of dengue fever induced by any dengue serotype occurring from 30 days post 2nd vaccination (Day 120) until end of Part 1 would provide at least 90% power to rule out vaccine effect of ≤25%.	
Comparison groups	Placebo (Part 1) v Tetravalent Dengue Vaccine (TDV) 0.5 mL (Part 1)

Number of subjects included in analysis	19021
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.001 [2]
Method	Cox Proportional Hazard Model
Parameter estimate	Vaccine Efficacy (VE)
Point estimate	80.2
Confidence interval	
level	95 %
sides	2-sided
lower limit	73.3
upper limit	85.3

Notes:

[1] - Statistical significance was concluded if the lower bound of the 95% CI for the VE was above 25%. Since the hypotheses was tested in a confirmatory manner at a 2-sided significance level of 5%, the calculated p-value was compared with 0.025.

[2] - VE and 95% CIs was estimated from Cox proportional hazard model with investigational product as a factor, adjusted for age, and stratified by region.

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Deaths and serious adverse events(SAEs):Parts1-2:All SAEs from Day 1 until end of Part 2;Part 3:All deaths,related SAEs or relevant SAEs in context of vaccine safety;Parts 4-5:All SAEs from Day 1b up to end of the trial.Non-serious AEs:Up to 28 days

Adverse event reporting additional description:

The data for adverse events is not reported as this is primary results posting and the study is ongoing, reporting adverse events may cause unblinding, therefore, the data will be reported at the time of final results posting.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Tetravalent Dengue Vaccine (TDV) 0.5 mL (Part 1)

Reporting group description:

TDV, 0.5mL, subcutaneous (SC) injection on Day 1 (Month 0) and Day 90 (Month 3) in Part 1 of the study.

Reporting group title	Placebo (Part 1)

Reporting group description:

Placebo-matching TDV, 0.5mL, subcutaneous (SC) injection on Day 1 (Month 0) and Day 90 (Month 3) in Part 1 of the study.

Serious adverse events	Tetravalent Dengue Vaccine (TDV) 0.5 mL (Part 1)	Placebo (Part 1)	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13380 (0.00%)	0 / 6687 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Tetravalent Dengue Vaccine (TDV) 0.5 mL (Part 1)	Placebo (Part 1)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 13380 (0.00%)	0 / 6687 (0.00%)	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: The data for adverse events is not reported as this is primary results posting and the study is ongoing, reporting adverse events may cause unblinding, therefore, the data will be reported at the

time of final results posting.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 November 2015	Following changes were implemented with Protocol Amendment 2: -The protocol was primarily amended to change the dosing regimen and to modify the long-term febrile surveillance methodology (during Part 3). -Updated the role of Data Monitoring Committee and addition of involvement of Adjudication Committee. -Added second trial vaccination on Day 90 (Month 3). -Updated time window between trial visits and specification of trial procedures for each year of follow-up during Part 3. -Updated trial objectives and endpoints. -Removed conditional booster. -Replacement of enhanced passive hospital-based surveillance by modified active surveillance. -Six-month cap on pre-vaccination surveillance for dengue replaced by 10 months. -Addition of febrile illness surveillance during dry-run. -Updated the section on collection of serious adverse events. -Specifications added on use of interactive web/voice response system (IWRS/IVRS) for subject enrollment/randomisation. -Updates to certain study procedures, statistical analysis, and eligibility criteria.
18 May 2020	Following changes were implemented with Protocol Amendment 4: -Added a booster phase to the ongoing DEN-301 trial. -Subheadings were generated to differentiate between Parts 1, 2, and 3 of the trial and the new booster phase of the trial (Parts 4 and 5). -Clarified that a dengue nonstructural protein 1 (NS1) antigen enzyme-linked immunosorbent assay (ELISA) was used for laboratory testing of febrile illness cases (suspected dengue cases). -Microneutralization test (MNT) was replaced with MNT50 for consistency. -The term 'Legally Authorized Representative (LAR)' was replaced by parent/guardian for consistency. -The administrative trial information was updated and minor grammatical and editorial changes were included.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported