23 July 2026
EMADOC-1700519818-3388007
Human Medicines Division

Assessment report for paediatric studies submitted in accordance with article 46 of regulation (EC) No 1901/2006

Qdenga

DENGUE TETRAVALENT VACCINE (LIVE, ATTENUATED)

Procedure no: EMA/PAM/0000334839

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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Status of this report and steps taken for the assessment			
Current step	**Description**	**Planned date**	**Actual Date**
☐	CHMP Rapporteur AR	28 April 2026	28 April 2026
☐	CHMP comments	11 May 2026	11 May 2026
☐	Updated CHMP Rapporteur AR	13 May 2026	13 May 2026
☐	Request of Supplementary Information	21 May 2026	21 May 2026
☐	Submission of responses	23 June 2026	23 June 2026
☐	Restart	24 June 2026	24 June 2026
☐	CHMP Rapporteur AR	08 July 2026	08 July 2026
☐	CHMP comments	13 July 2026	13 July 2026
☐	Updated CHMP Rapporteur AR	16 July 2026	16 July 2026
☒	CHMP outcome	23 July 2026	23 July 2026

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1. Introduction

On 27 February 2026, the MAH submitted a completed paediatric study for Qdenga, in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

The MAH stated that study DEN-302 is a stand-alone study.

2.2. Information on the pharmaceutical formulation used in the study

The pharmaceutical formulation used in the study was the approved TDV (Qdenga) product, which is indicated for the prevention of dengue disease in individuals from 4 years of age. The dose regimen consists of 2 subcutaneous (SC) doses of 0.5 mL TDV administered at Month 0 and Month 3.

2.3. Clinical aspects

2.3.1. Introduction

The MAH submitted a final report for:

- DEN-302, a phase 3, randomized, multi-center, double-blind, placebo-controlled trial to evaluate the safety and immunogenicity of a 2-dose schedule of TDV administered by SC injection in healthy participants aged 4 to 60 years in India

2.3.2. Clinical study

DEN-302, a phase 3, randomized, multi-center, double-blind, placebo-controlled trial to evaluate the safety and immunogenicity of a 2-dose schedule of TDV administered by SC injection in healthy participants aged 4 to 60 years in India.

Description

This is a Stand-alone Post-Authorization Measure (PAM) submission to address Article 46 of the EU Paediatric Regulation. Trial DEN-302 was a phase 3, randomized, multi-centre, double-blind, placebo-controlled trial to evaluate the safety and immunogenicity of a 2-dose schedule of TDV administered by SC injection in healthy participants aged 4 to 60 years in India.

The trial was completed (last subject's last visit/contact) on 05 May 2025.

Trial DEN-302 was conducted in accordance with the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, Harmonised Tripartite Guideline and Good Clinical Practice (ICH E6-GCP), ethical principles that have their origin in the Declaration of Helsinki, and applicable local regulatory requirements.

Methods

Study participants

A total of 480 participants were enrolled and randomized in parallel in 2 cohorts:

- Cohort 1 (adults ≥18-≤60 years of age): 240 adults were enrolled and randomly assigned (3:1) to receive either TDV (N = 180) or placebo (N = 60).
- Cohort 2 (children and adolescents ≥4-<18 years of age): 240 children and adolescents were enrolled and randomly assigned (3:1) to receive either TDV (N = 180) or placebo (N = 60).

Treatments

Children, adolescents, and adults received, by SC injection, in a random assignment of 3:1, TDV or placebo on Day 1 and the second dose of TDV or placebo 3 months later. Of these, 180 participants in each cohort received TDV (360 participants in total), and 60 participants in each cohort received placebo (120 participants in total).

Participants were followed up for immunogenicity and safety assessments for 6 months after the second vaccination, i.e., from Day 90 (Month [M] 3), through Day 270 (M9), or end of trial. The trial duration was approximately 270 days (9 months) for each participant.

Up to 4 blood samples were taken throughout the trial. During the trial, participants visited the trial clinic on 6 occasions.

Lyophilized TDV was reconstituted by adding diluent (37 mM sodium chloride) prior to SC injection.

- (TDV) and
- (sodium chloride [37 mM] solution diluent)

Dosing schedule:

2 single doses of TDV or 2 single doses of placebo given 3 months (ie, 90 days) apart (at Day 1 [M0] and Day 90 [M3]), applicable to both cohorts.

Placebo:

The placebo was normal saline for injection (0.9% sodium chloride [saline] solution) presented as single dose units for 0.5 mL dosing.

Objectives

<u>Primary Objectives</u>

Safety

• To assess the safety profile of TDV administered as 2 doses given 3 months apart in healthy adults, adolescents, and children.

Immunogenicity

• To evaluate the immunogenicity of TDV administered as 2 doses given 3 months apart in healthy adults, adolescents, and children at 1 month post second dose.

<u>Secondary Objectives</u>

Immunogenicity

• To describe immunogenicity of TDV at baseline and 6 months post second TDV dose when administered as 2 doses given 3 months apart.

• To describe seropositivity (% of participants with reciprocal neutralizing titer ≥10) at baseline, 1 month post second TDV dose, and 6 months post second TDV dose.

Outcomes/endpoints

Primary Endpoints

Safety

- Frequency and severity of solicited local (injection site) AEs for 7 days (day of vaccination + 6 subsequent days) and solicited systemic AEs for 14 days (day of vaccination + 13 subsequent days) postvaccination at Day 1 (M0) and Day 90 (M3).
- Percentage of participants with any unsolicited AEs for 28 days (day of vaccination + 27 subsequent days) postvaccination at Day 1 (M0) and Day 90 (M3).
- Percentage of participants with an AE leading to participant discontinuation from the trial from Day 1 (M0) postvaccination through the end of the trial.
- Percentage of participants with an AE leading to TDV or placebo withdrawal from Day 1 (M0) postvaccination through the end of the trial.
- Percentage of participants with a MAAE from Day 1 (M0) postvaccination through the end of the trial.
- Percentage of participants with a SAE from Day 1 (M0) postvaccination through the end of the trial.

Immunogenicity

- Geometric mean titers (GMTs) of neutralizing antibodies (by microneutralization test [MNT]) against each of the 4 dengue virus serotypes at Day 120 (M4).

Secondary Endpoints

Immunogenicity

- GMTs by MNT against each of the 4 dengue virus serotypes at Day 1 (M0) and Day 270 (M9).
- Seropositivity rates (% of participants with reciprocal neutralizing titer ≥10) against each of the 4 dengue virus serotypes at Day 1 (M0), Day 120 (M4), and Day 270 (M9).
- Seropositivity rates (% of participants with reciprocal neutralizing titer ≥10) against multiple (2, 3, or 4) dengue virus serotypes at Day 1 (M0), Day 120 (M4), and Day 270 (M9).

Exploratory Endpoint

Comparison of GMTs (by MNT) and geometric mean ratio (GMR) between Cohort 1 versus Cohort 2, against each of the 4 dengue virus serotypes at Day 1 (M0), Day 120 (M4), and Day 270 (M9) for baseline seronegative participants.

Note: this analysis was performed for GMRs derived by dividing the Cohort 2 GMTs by Cohort 1 GMTs.

Sample size

Trial analysis was designed to be descriptive and was not based on testing formal null hypotheses. A sample size of 180 participants received TDV in each cohort (N = 360 in total) 60 participants received placebo in each cohort (N = 120 in total), as per the random assignment of 3:1 (TDV:placebo). Therefore, the total trial sample size was 480 participants.

Randomisation and blinding (masking)

Randomisation

The investigator or designee accessed the interactive response technology (IRT) system at participant enrollment (Day -28 [M -1]) to obtain the participant number. This number was used throughout the trial.

All trial kits (TDV/placebo) were provided by the sponsor in a uniquely numbered carton and dispensed in a masked manner by IRT. The investigator or designee accessed the IRT at each dispensing visit to obtain the Vaccine Identification number for the vaccine dose (TDV or placebo).

TDV or placebo was administered by unblinded personnel qualified to perform that function under applicable laws and regulations for this trial.

Blinding

This was a double-blind trial; the investigator and participants were masked to TDV or placebo assignment. The trial masking was maintained using IRT. One or more designated pharmacists/vaccine administrators at each site were not masked to the randomly assigned treatment. These personnel had no role in data collection or evaluation, but they were responsible for receiving and storing the trial vaccines to ensure that the trial blind was not revealed.

Statistical Methods

Statistical analyses were performed on different analysis sets. The Randomized Set included all randomized participants, regardless of whether a dose of TDV or placebo was received. The Safety Analysis Set included all participants who received at least 1 dose of TDV or placebo. The Full Analysis Set (FAS) included all randomized participants who received at least 1 dose of TDV or placebo and for whom a valid pre-dose (baseline) measurement and at least 1 valid post-dose measurement were received for immunogenicity assessments. The Per-Protocol Analysis Set (PPS) included all participants from the FAS who had no major protocol violations. Primary and secondary endpoints were summarized based on the PPS; supportive analyses were provided based on the FAS. Demographic characteristics were summarized descriptively based on the Safety Analysis Set, FAS, and PPS.

Results

Participant flow and recruitment

Five hundred forty-one potential participants were screened, of whom 480 (88.7%) were randomly assigned. Sixty-one (11.3%) participants were not eligible for random assignment because 48 (78.7%) were screen failures and 13 (21.3%) withdrew from proceeding further in the trial.

Of the 480 participants who were randomly assigned, all (100%) participants received at least 1 dose of either TDV or placebo: 473 (98.5%) received 2 doses, and 470 (97.9%) completed the trial.

A total of 7 (1.5%) participants prematurely discontinued from a second dose of TDV or placebo because they were: lost to follow-up (n = 3), withdrew from the trial (n = 3), or experienced an adverse event (AE) (n = 1).

A total of 10 (2.1%) participants prematurely discontinued from the trial because they were: lost to follow-up (n = 4), withdrew from the trial (n = 3), experienced an AE (n = 1) (there was no unmasking for this participant at the time of discontinuation due to AE), or discontinued for other reason(s) (n = 2).

Of the 240 randomly assigned adult participants (Cohort 1), 235 (97.9%) received 2 doses of either TDV or placebo, and 234 (97.5%) completed the trial. Five (2.1%) participants prematurely withdrew prior to the second vaccination dose (4 [2.2%] TDV recipients and 1 [1.7%] placebo recipient). Reasons were lost to follow-up, withdrawal by participant, or AE. A total of 6 (2.5%) participants prematurely discontinued from the trial (5 [2.8%] TDV recipients and 1 [1.7%] placebo recipient). Reasons were lost to follow-up, withdrawal by participant, adverse event, or other reasons (n=1, where the participant was traveling).

Of the 240 randomly assigned children and adolescents (Cohort 2), 238 (99.2%) received 2 doses of either TDV or placebo, and 236 (98.3%) completed the trial. A total of 2 (0.8%) participants prematurely withdrew prior to the second vaccination (1 [0.6%] TDV recipient was lost to follow-up and 1 [1.7%] placebo recipient withdrew from the second dose). A total of 4 (1.7%) participants prematurely discontinued from the trial (2 [1.1%] TDV recipients and 2 [3.3%] placebo recipients). Participants discontinued from the trial because of lost to follow-up, withdrawal by participant, or other reasons (n = 1, where the participant relocated to another city).

Baseline data

Demographic and baseline characteristics for the Safety Analysis Set are presented in Table 1. Demographic and baseline characteristics across the FAS, PPS, and safety analysis sets were similar.

Adults in this trial were on average 37.0 years old, and all were Asian Indian (100%). The children and adolescents were on average 9.8 years old and were also all Asian Indian ([99.6%] (race was not reported for 1 participant). The trial enrolled male participants primarily, especially in the adult cohort (71.7% males).

91.5% of the overall trial participants were dengue seropositive at baseline and baseline tetravalent seropositivity was 79.6%. The demographic characteristics were generally comparable between TDV and placebo groups.

Between the PPS/FAS and Safety sets there was a difference of only 8 participants (5 adults, 3 children and adolescents). Therefore, only a marginal difference was observed in the evaluated variables.

Table 1 Summary of Demographic and Baseline Characteristics (Safety Analysis Set)

	Participants (TDV and Placebo) Number (%) of Participants		
	≥4-<18 Years (N = 240)	≥18-≤60 Years (N = 240)	≥4-≤60 Years (N = 480)
Age (years) [a]			
Mean (SD)	9.8 (4.12)	37.0 (11.51)	23.4 (16.12)
Sex (n [%])			
Male participants	132 (55.0)	172 (71.7)	304 (63.3)
Female participants	108 (45.0)	68 (28.3)	176 (36.7)
Race (n [%])			
Asian	239 (99.6)	240 (100)	479 (99.8)
Asian Indian	239 (100)	240 (100)	479 (100)
Not reported [b]	1 (0.4)	0	1 (0.2)
BMI (kg/m^2) [c]			
N	240	240	480
Mean (SD)	16.90 (3.952)	24.78 (3.443)	20.84 (5.409)
Median	15.85	24.60	20.90
Minimum, maximum	10, 34.5	14.9, 34.6	10, 34.6
Baseline serostatus for Dengue			
N evaluated	240	240	480
Seropositive [d]	214 (89.2)	225 (93.8)	439 (91.5)
Seronegative [e]	26 (10.8)	15 (6.3)	41 (8.5)

Source: Table 15.1.8.2.
BMI: Body Mass Index; TDV: Tetravalent Dengue Vaccine.
[a] Age was calculated relative to the date of informed consent.
[b] Participant who refused to identify their race was coded as "not reported".
[c] BMI was auto-calculated using baseline weight and height measurements.
[d] Seropositive for dengue is defined as reciprocal neutralizing antibody titer ≥10 for any of the 4 dengue serotypes.
[e] Seronegative for dengue is defined as reciprocal neutralizing antibody titer <10 for all dengue serotypes.

Number analysed

Immunogenicity results

Primary Endpoint

The primary immunogenicity endpoint was the GMTs of dengue neutralizing antibodies (derived from dengue MNT results) against each of the 4 dengue virus serotypes (DENV-1, DENV-2, DENV-3, DENV-4) at Day 120 (M4).

In this largely seropositive population, TDV elicited robust immune responses in healthy adults, children, and adolescents, with higher neutralizing antibody titers at Day 120 (M4) than at baseline against all 4 dengue serotypes (Figure 1, Table 2).

- Overall population: Most participants included in the PPS were seropositive for dengue at baseline: 431/472 (91.3%); the remainder 41/472 (8.7%) were seronegative at baseline. GMTs of dengue neutralizing antibodies increased between baseline and Day 120 (M4) for all dengue serotypes in the overall population from the TDV and placebo groups (PPS). GMTs of dengue neutralizing antibodies were higher in the TDV group compared with placebo for all 4 dengue serotypes.
- Adults: Most adults included in the PPS were seropositive for dengue at baseline: 220/235 (93.6%) seropositive, 15/235 (6.4%) seronegative. An increase in GMTs of dengue neutralizing antibodies for adults was observed between baseline and Day 120 (M4) for all dengue serotypes in the TDV group versus placebo. GMTs of dengue neutralizing antibodies at Day 120 were higher in the TDV group compared with placebo for all 4 dengue serotypes.
- Children and adolescents: Most children and adolescents included in the PPS were seropositive for dengue at baseline: 211/237 (89.0%) seropositive, 26/237 (11.0%) seronegative. An increase in GMTs of dengue neutralizing antibodies was observed between baseline and Day 120 (M4) for all dengue serotypes in the TDV group versus placebo. GMTs of dengue neutralizing antibodies at Day 120 were higher for the TDV group than for the placebo group for all 4 dengue serotypes. GMTs at Day 120 varied between either DENV-1 or DENV-2, being the highest followed by DENV-3 and DENV-4. Supportive analysis on the FAS revealed results reflective of those seen for the PPS for the primary endpoint.

Table 2 Geometric Mean Titers of Neutralizing Antibodies Measured by MNT for Each Dengue Serotype, by Visit, for the Overall Population, Adults and Children and Adolescents– Per-Protocol Analysis Set

Serotype	Summary Statistics	Overall				Adults				Children and Adolescents			
		Baseline		Day 120 (Month 4)		Baseline		Day 120 (Month 4)		Baseline		Day 120 (Month 4)	
		TDV (N = 354)	Placebo (N = 118)	TDV (N = 354)	Placebo (N = 118)	TDV (N = 176)	Placebo (N = 59)	TDV (N = 176)	Placebo (N = 59)	TDV (N = 178)	Placebo (N = 59)	TDV (N = 178)	Placebo (N = 59)
DENV-1	N evaluated	354	118	301	103	176	59	144	50	178	59	157	53
	Geometric mean (SD)	611.3 (13.04)	395.2 (15.23)	2961.0 (4.73)	482.7 (13.37)	1038.5 (10.63)	699.8 (12.42)	3072.4 (4.80)	864.5 (11.49)	362.0 (14.27)	223.1 (16.76)	2862.4 (4.68)	278.6 (13.92)
	95% CI	(467.4, 799.5)	(240.5, 649.2)	(2482.7, 3531.4)	(290.8, 801.3)	(730.6, 1476.3)	(362.9, 1349.4)	(2373.1, 3977.6)	(431.9, 1730.4)	(244.3, 536.4)	(107.0, 465.2)	(2244.1, 3651.2)	(134.8, 575.7)
DENV-2	N evaluated	354	118	301	103	176	59	144	50	178	59	157	53
	Geometric mean (SD)	576.7 (11.60)	380.2 (16.09)	2653.6 (3.91)	554.1 (12.79)	797.9 (9.95)	460.1 (13.63)	2530.9 (4.11)	952.5 (9.56)	418.4 (12.92)	314.1 (19.00)	2771.3 (3.74)	332.4 (15.16)
	95% CI	(446.4, 745.1)	(229.1, 630.8)	(2273.5, 3097.2)	(336.7, 911.9)	(566.9, 1123.1)	(232.9, 908.8)	(2005.5, 3194.0)	(501.4, 1809.5)	(286.5, 610.9)	(145.8, 676.6)	(2251.1, 3411.6)	(157.1, 703.2)
DENV-3	N evaluated	354	118	300	103	176	59	144	50	178	59	156	53
	Geometric mean (SD)	382.9 (10.86)	306.4 (14.10)	1634.5 (4.81)	341.4 (11.87)	618.9 (9.23)	463.9 (10.91)	1663.3 (4.76)	571.9 (8.26)	238.2 (11.60)	202.4 (17.11)	1608.2 (4.89)	209.9 (14.94)
	95% CI	(298.4, 491.3)	(189.2, 496.4)	(1367.2, 1954.0)	(210.5, 553.7)	(444.6, 861.4)	(248.9, 864.6)	(1286.5, 2150.5)	(313.9, 1042.0)	(165.7, 342.2)	(96.6, 424.3)	(1251.2, 2067.2)	(99.6, 442.2)
DENV-4	N evaluated	354	118	301	103	176	59	144	50	178	59	157	53
	Geometric mean (SD)	255.2 (9.68)	201.4 (13.80)	1034.5 (4.21)	218.2 (9.33)	392.4 (8.61)	275.3 (10.61)	1079.6 (4.23)	351.0 (7.16)	166.8 (10.05)	147.3 (17.29)	994.9 (4.20)	139.3 (10.90)
	95% CI	(201.3, 323.6)	(124.8, 325.0)	(878.9, 1217.7)	(141.0, 337.6)	(284.8, 540.6)	(148.8, 509.4)	(851.2, 1369.2)	(200.6, 614.3)	(118.6, 234.7)	(70.1, 309.6)	(793.3, 1247.6)	(72.1, 269.1)

CI: confidence interval; DENV: dengue virus; MNT: microneutralization test; SD: standard deviation; TDV: dengue tetravalent vaccine (live, attenuated), also known as TAK-003.
N evaluated is the number of participants with available values within the relevant visit window.
Geometric mean (SD) and 95% CI are calculated based on the natural log-transformed titers and anti-log values are displayed.
Dengue neutralizing antibody titers (MNT) that were below the lower limit of detection (LLOD, 10) are imputed with a value of 5 (half of the LLOD). Reported values ≥ the LLOD and < the lower limit of quantitation (LLOQ; DENV-1 = 29, DENV-2 = 13, DENV-3 = 18, DENV-4 = 17) are imputed with the mid-point between the LLOD and LLOQ.
Baseline refers to the last valid measurement prior to first vaccination.

Secondary Endpoints

- In this largely seropositive population, immune response, seropositivity rate against individual serotypes, and at least trivalent and tetravalent seropositivity rates were consistently higher for adults, children, and adolescents receiving TDV, between baseline and 6 months post second dose (Day 270 [M9]).

- Seropositivity rates for DENV (1-4) at Day 1 (M0), Day 120 (M4), and Day 270 (M9) (PPS):

– Overall population: DENV (1-4) serotype seropositivity for TDV recipients ranged from 99.3% to 99.7% at Day 120 and remained between 93.7% to 99.1% at Day 270 versus 80.6% to 84.5% and 75.2% to 87.2% for placebo recipients, respectively.

– Adults: DENV (1-4) serotype seropositivity for TDV recipients ranged from 98.6% to 99.3% at Day 120 and remained between 95.1% to 99.4% at Day 270 versus 86.0% to 90.0% and 76.8% to 89.3% for placebo recipients, respectively.

– Children and adolescents: DENV (1-4) serotype seropositivity for TDV recipients was 100% for all serotypes at Day 120 and remained between 92.2% to 99.4% at Day 270 versus 71.7% to 83.0% and 73.6% to 84.9% for placebo recipients, respectively.

- Seropositivity rates against multiple (2, 3, or 4) dengue virus serotypes at Day 1 (M0), Day 120 (M4), and Day 270 (M9) (PPS):

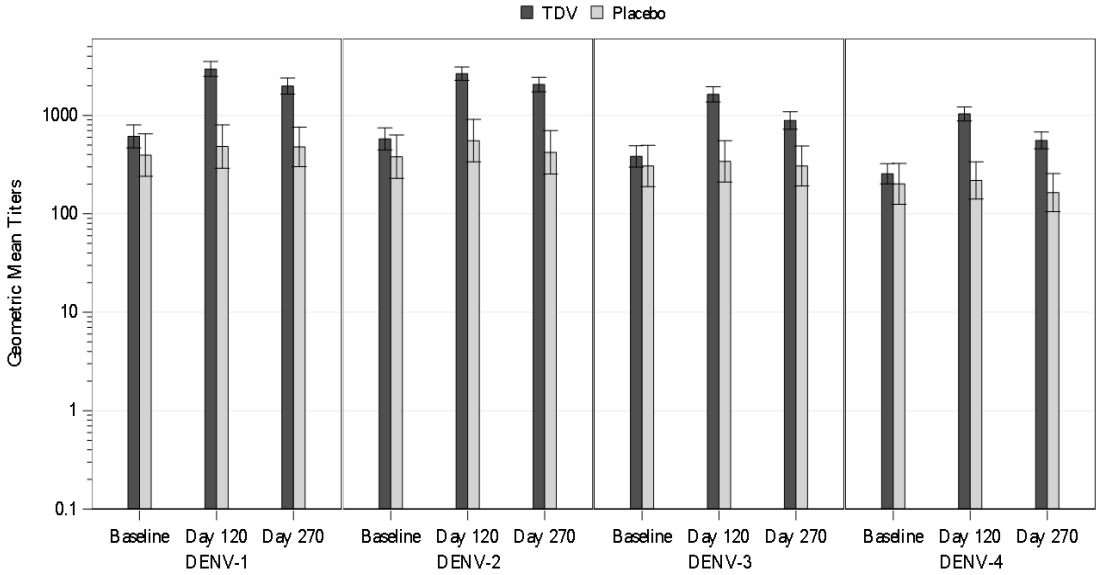
– Overall Population: At least trivalent seropositivity for TDV recipients was 99.3% at Day 120 and remained at 97.6% at Day 270 versus 78.6% and 78.0% for placebo recipients, respectively. Tetravalent seropositivity for TDV recipients was 98.7% at Day 120 and remained at 92.4% at Day 270 versus 78.6% and 75.2% for placebo recipients, respectively.

– Adults: At least trivalent seropositivity for TDV recipients was 98.6% at Day 120 and remained at 98.2% at Day 270 versus 86.0% and 82.1% for placebo recipients, respectively. Tetravalent seropositivity for TDV recipients was 97.9% at Day 120 and remained at 93.9% at Day 270 versus 86.0% and 76.8% for placebo recipients, respectively.

– Children and adolescents: At least trivalent seropositivity for TDV recipients was 100% at Day 120 and remained at 97.0% at Day 270 versus 71.7% and 73.6% for placebo recipients, respectively. Tetravalent seropositivity for children and adolescents from the TDV group was 99.4% at Day 120 and remained at 91.0% at Day 270 versus 71.7% and 73.6% for placebo recipients, respectively.

Figure 1 presents GMTs of dengue neutralizing antibodies (derived from dengue MNT results) for each of the 4 dengue virus serotypes (DENV-1, DENV-2, DENV-3, DENV-4) at baseline, Day 120 (M4), and at Day 270 (M9). Between baseline and Day 270 (M9), GMTs increased for all 4 dengue serotypes in the TDV group versus placebo. At Day 270, GMTs were highest for DENV-1 or DENV-2, followed by DENV-3 and then DENV-4.

Figure 1 Geometric Mean Titers of Neutralizing Antibodies for Each Dengue Serotype, Over Time, for Participants ≥4 to ≤60 Years – Per-Protocol Analysis Set



DENV: dengue virus; TDV: Tetravalent Dengue Vaccine, also known as TAK-003.
Log_{10} scale is used. The error bars represent the corresponding 95% CIs of the GMTs.
Baseline refers to the last valid measurement prior to first vaccination.

Exploratory Endpoint

- The exploratory immunogenicity comparison between children and adolescents versus adults at baseline, 1 month, and 6 months post second TDV dose was limited by insufficient baseline seronegative participants. However, for baseline seropositive TDV recipients, GMTs for each of the 4 dengue virus serotypes at Day 120 (M4) for children and adolescents versus adults were comparable.

Immunogenicity Conclusions

In this largely seropositive population, TDV demonstrated a robust immune response in healthy adults, children and adolescents with higher neutralizing antibodies at Day 120 (M4) and Day 270 (M9) than at baseline against each of the 4 dengue serotypes.

Because of the paucity of seronegative participants in this trial, caution is warranted when interpreting data for these participants. An immune response across all 4 serotypes, nevertheless, was demonstrated regardless of baseline serostatus.

Safety results

An overview of AEs for all participants in the Safety Analysis Set is presented in Table 3

Table 3 Overview of Any Adverse Events – Participants ≥4 to ≤60 Years (Safety Analysis Set)

	Number (%) of Participants					
	After Any Vaccination		After First Vaccination		After Second Vaccination	
	TDV N = 360	Placebo N = 120	TDV N = 360	Placebo N = 120	TDV N = 355	Placebo N = 118
Solicited AEs [a]						
Within 30 min of vaccination [b]	41/360 (11.4)	10/120 (8.3)	41/360 (11.4)	10/120 (8.3)	2/355 (0.6)	0
Local AEs [c]	73/358 (20.4)	21/120 (17.5)	58/358 (16.2)	16/120 (13.3)	31/354 (8.8)	8/118 (6.8)
Systemic AEs [d]	49/358 (13.7)	15/120 (12.5)	37/358 (10.3)	12/120 (10)	18/354 (5.1)	3/118 (2.5)
Related	40/358 (11.2)	14/120 (11.7)	29/358 (8.1)	11/120 (9.2)	16/354 (4.5)	3/118 (2.5)
Prolonged solicited AEs [e]	1/360 (0.3)	0	1/360 (0.3)	0	0	0
Local	1/360 (0.3)	0	1/360 (0.3)	0	0	0
Systemic	0	0	0	0	0	0
Unsolicited AEs [f]	19 (5.3)	6 (5.0)	8 (2.2)	2 (1.7)	11 (3.1)	4 (3.4)
Mild	16 (4.4)	4 (3.3)	5 (1.4)	2 (1.7)	11 (3.1)	2 (1.7)
Moderate	2 (0.6)	2 (1.7)	2 (0.6)	0	0	2 (1.7)
Severe [g]	1 (0.3)	0	1 (0.3)	0	0	0
Related to TDV or placebo	5 (1.4)	0	3 (0.8)	0	2 (0.6)	0
Related to trial procedure	0	0	0	0	0	0
TDV/placebo withdrawal [h]	1 (0.3)	0	1 (0.3)	0	0	0
Leading to discontinuation from trial [h]	1 (0.3)	0	1 (0.3)	0	0	0
Medically attended	6 (1.7)	3 (2.5)	3 (0.8)	1 (0.8)	3 (0.8)	2 (1.7)
Medically attended AEs	46 (12.8)	14 (11.7)	27 (7.5)	10 (8.3)	20 (5.6)	4 (3.4)
Mild	41 (11.4)	12 (10.0)	24 (6.7)	10 (8.3)	17 (4.8)	2 (1.7)
Moderate	4 (1.1)	2 (1.7)	2 (0.6)	0	3 (0.8)	2 (1.7)
Severe [g]	1 (0.3)	0	1 (0.3)	0	0	0
Related to TDV or placebo	0	0	0	0	0	0
Related to trial procedure	0	0	0	0	0	0
TDV/placebo withdrawal [h]	1 (0.3)	0	1 (0.3)	0	0	0
Leading to discontinuation from trial [h]	1 (0.3)	0	1 (0.3)	0	0	0
Serious AEs	0	0	0	0	0	0
Deaths	0	0	0	0	0	0

AEs: adverse events; min: minutes; TDV: Tetravalent Dengue Vaccine, also known as TAK-003.

[a] Percentages for solicited AEs are based on the number of participants evaluated - mentioned in the respective denominator.

[b] In-clinic assessment.

[c] Within 7 days after vaccination.

[d] Within 14 days after vaccination.

[e] Solicited local or systemic AEs that continued after Day 7 and Day 14, respectively. A 41-year-old female participant experienced non-serious mild erythema the next day after the first TDV dose. The event resolved by Day 9, and it was considered related to vaccination.
[f] Up to 28 days after vaccination.
[g] A 24-year-old male participant experienced severe, non-serious, unrelated headache after the first TDV dose. The event resolved 6 days later.
[h] A 49-year-old male participant experienced non-serious moderate pharyngitis the next day after the first TDV dose. The event resolved 40 days later but the participant withdrew from receiving the second TDV dose and discontinued from the trial. The event was considered not related to vaccine administration.

Adverse events withing the 30 minutes after vaccination

Within the 30 minutes after any vaccination, 41 (11.4%) participants from the TDV group and 10 (8.3%) from the placebo group experienced mild pain. There were no solicited systemic AEs reported within 30 minutes after vaccination (assessed in the clinic).

Local Adverse events within 7 days after any vaccination

Seventy-three (20.4%) TDV recipients and 21 (17.5%) placebo recipients experienced solicited local AEs within 7 days after any vaccination. All solicited local AEs reported within 7 days after any vaccination were mild or moderate in severity. Fewer local AEs were reported after the second vaccination than after the first vaccination.

The percentage of adults (≤18-≤60 yoa) reporting solicited local AEs within 7 days after any vaccination was 19.6% and 13.3%, in the TDV and placebo groups, respectively. The percentage of children and adolescents (≥4-<18 yoa) reporting solicited local AEs within 7 days after any vaccination was 17.3% and 20.0% in the TDV and placebo groups, respectively.

Table 4 Summary of Solicited Local Adverse Events Within 7 Days Postvaccination (Adults >18 -< 60 Years) - Safety Analysis Set

	Number (%) of Participants					
	After Any Vaccination (N = 240)		After First Vaccination (N = 240)		After Second Vaccination (N = 235)	
	TDV (N = 180)	Placebo (N = 60)	TDV (N = 180)	Placebo (N = 60)	TDV (N = 176)	Placebo (N = 59)
Any solicited local AEs						
N evaluated	179 (99.4)	60 (100)	179 (99.4)	60 (100)	176 (100)	59 (100)
Any	35 (19.6)	8 (13.3)	29 (16.2)	7 (11.7)	13 (7.4)	4 (6.8)
Mild	32 (17.9)	7 (11.7)	27 (15.1)	7 (11.7)	12 (6.8)	3 (5.1)
Moderate	3 (1.7)	1 (1.7)	2 (1.1)	0	1 (0.6)	1 (1.7)
Severe	0	0	0	0	0	0
Pain						
N evaluated	179 (99.4)	60 (100)	179 (99.4)	60 (100)	176 (100)	59 (100)
Any	33 (18.4)	8 (13.3)	27 (15.1)	7 (11.7)	13 (7.4)	4 (6.8)
Mild	30 (16.8)	7 (11.7)	25 (14.0)	7 (11.7)	12 (6.8)	3 (5.1)
Moderate	3 (1.7)	1 (1.7)	2 (1.1)	0	1 (0.6)	1 (1.7)
Severe	0	0	0	0	0	0
Erythema						
N evaluated	179 (99.4)	60 (100)	179 (99.4)	60 (100)	176 (100)	59 (100)
Any	2 (1.1)	0	2 (1.1)	0	0	0
Mild	2 (1.1)	0	2 (1.1)	0	0	0
Moderate	0	0	0	0	0	0
Severe	0	0	0	0	0	0
Swelling						
N evaluated	179 (99.4)	60 (100)	179 (99.4)	60 (100)	176 (100)	59 (100)
Any	0	0	0	0	0	0
Mild	0	0	0	0	0	0
Moderate	0	0	0	0	0	0
Severe	0	0	0	0	0	0

Source: Table 15.3.1.1.1.2.
TDV: Tetravalent Dengue Vaccine.
Percentages are based on the total number of participants with non-missing data (N evaluated) for each event.
Percentage of N evaluated is based on the number of participants in the Safety Analysis Set who received the specific trial vaccination.
Participants were counted once per AE based on the highest severity category exclusively.
Records with implausible values are excluded from analysis if they do not fall within the following values: Erythema ≤50 cm; Swelling ≤50 cm.

Table 5 Summary of Solicited Local Adverse Events Within 7 Days Postvaccination (Children and Adolescents >4 -< 18 Years) - Safety Analysis Set

	Number (%) of Participants					
	After Any Vaccination (N = 240)		After First Vaccination (N = 240)		After Second Vaccination (N = 238)	
	TDV (N = 180)	Placebo (N = 60)	TDV (N = 180)	Placebo (N = 60)	TDV (N = 179)	Placebo (N = 59)
Any solicited local AEs						
N evaluated	179 (99.4)	60 (100)	179 (99.4)	60 (100)	178 (99.4)	59 (100)
Any	31 (17.3)	12 (20.0)	19 (10.6)	8 (13.3)	17 (9.6)	4 (6.8)
Mild	29 (16.2)	12 (20.0)	18 (10.1)	8 (13.3)	16 (9.0)	4 (6.8)
Moderate	2 (1.1)	0	1 (0.6)	0	1 (0.6)	0
Severe	0	0	0	0	0	0
Pain						
N evaluated	179 (99.4)	60 (100)	179 (99.4)	60 (100)	178 (99.4)	59 (100)
Any	30 (16.8)	12 (20.0)	18 (10.1)	8 (13.3)	17 (9.6)	4 (6.8)
Mild	28 (15.6)	12 (20.0)	17 (9.5)	8 (13.3)	16 (9.0)	4 (6.8)
Moderate	2 (1.1)	0	1 (0.6)	0	1 (0.6)	0
Severe	0	0	0	0	0	0
Erythema						
N evaluated	179 (99.4)	60 (100)	179 (99.4)	60 (100)	178 (99.4)	59 (100)
Any	0	0	0	0	0	0
Mild	0	0	0	0	0	0
Moderate	0	0	0	0	0	0
Severe	0	0	0	0	0	0
Swelling						
N evaluated	179 (99.4)	60 (100)	179 (99.4)	60 (100)	178 (99.4)	59 (100)
Any	2 (1.1)	0	2 (1.1)	0	0	0
Mild	2 (1.1)	0	2 (1.1)	0	0	0
Moderate	0	0	0	0	0	0
Severe	0	0	0	0	0	0

Source: Table 15.3.1.1.1.2.
TDV: Tetravalent Dengue Vaccine.
Percentages are based on the total number of participants with non-missing data (N evaluated) for each event.
Percentage of N evaluated is based on the number of participants in the Safety Analysis Set who received the specific trial vaccination.
Participants were counted once per AE based on the highest severity category exclusively.
Records with implausible values are excluded from analysis if they do not fall within the following values: Erythema ≤50 cm; Swelling ≤50 cm.

A prolonged solicited local AE (i.e., AE continuing beyond Day 7) was reported by a single TDV recipient (1 [0.3%]) after any vaccination. The 41-year-old female participant experienced non-serious mild erythema the next day after the first TDV dose. The event resolved by Day 9, and it was considered related to vaccination

Systemic Adverse Events within 14 days after any vaccination

Forty-nine (13.7%) TDV recipients and 15 (12.5%) placebo recipients experienced solicited systemic AEs within 14 days (day of vaccination + 13 subsequent days) after any vaccination. Most solicited systemic AEs reported within 14 days after any vaccination were mild or moderate.

The percentage of adults (≤18-≤60 yoa) reporting solicited systemic AEs after any vaccination was 16.8% and 18.3% in the TDV and placebo groups, respectively. The percentage of children and adolescents (≥4-<18 yoa) reporting solicited systemic AEs after any vaccination was 13.4% and 10.0% in the TDV and placebo groups, respectively.

Table 6 Summary of Solicited Systemic Adverse Events Within 14 Days Postvaccination (Adults >18 -< 60 Years) - Safety Analysis Set

	Number (%) of Participants					
	After Any Vaccination (N = 240)		After First Vaccination (N = 240)		After Second Vaccination (N = 235)	
	TDV (N = 180)	Placebo (N = 60)	TDV (N = 180)	Placebo (N = 60)	TDV (N = 176)	Placebo (N = 59)
Any solicited systemic AEs						
N evaluated	179 (99.4)	60 (100)	179 (99.4)	60 (100)	176 (100)	59 (100)
Any *	29 (16.2)	9 (15.0)	22 (12.3)	8 (13.3)	9 (5.1)	1 (1.7)
Mild	22 (12.3)	8 (13.3)	18 (10.1)	7 (11.7)	6 (3.4)	1 (1.7)
Moderate	5 (2.8)	1 (1.7)	2 (1.1)	1 (1.7)	3 (1.7)	0
Severe	2 (1.1)	0	2 (1.1)	0	0	0
Headache						
N evaluated	179 (99.4)	60 (100)	179 (99.4)	60 (100)	176 (100)	59 (100)
Any	19 (10.6)	6 (10.0)	14 (7.8)	6 (10.0)	7 (4.0)	0
Mild	15 (8.4)	6 (10.0)	11 (6.1)	6 (10.0)	6 (3.4)	0
Moderate	2 (1.1)	0	1 (0.6)	0	1 (0.6)	0
Severe	2 (1.1)	0	2 (1.1)	0	0	0
Asthenia						
N evaluated	179 (99.4)	60 (100)	179 (99.4)	60 (100)	176 (100)	59 (100)
Any	15 (8.4)	5 (8.3)	11 (6.1)	4 (6.7)	4 (2.3)	1 (1.7)
Mild	14 (7.8)	5 (8.3)	11 (6.1)	4 (6.7)	3 (1.7)	1 (1.7)
Moderate	1 (0.6)	0	0	0	1 (0.6)	0
Severe	0	0	0	0	0	0
Malaise						
N evaluated	179 (99.4)	60 (100)	179 (99.4)	60 (100)	176 (100)	59 (100)
Any	8 (4.5)	3 (5.0)	5 (2.8)	3 (5.0)	3 (1.7)	0
Mild	8 (4.5)	3 (5.0)	5 (2.8)	3 (5.0)	3 (1.7)	0
Moderate	0	0	0	0	0	0
Severe	0	0	0	0	0	0
Myalgia						
N evaluated	179 (99.4)	60 (100)	179 (99.4)	60 (100)	176 (100)	59 (100)
Any	14 (7.8)	4 (6.7)	11 (6.1)	4 (6.7)	3 (1.7)	0
Mild	11 (6.1)	3 (5.0)	10 (5.6)	3 (5.0)	1 (0.6)	0
Moderate	3 (1.7)	1 (1.7)	1 (0.6)	1 (1.7)	2 (1.1)	0
Severe	0	0	0	0	0	0

Table 12.e Summary of Solicited Systemic Adverse Events Within 14 Days Postvaccination (Adults ≥18-≤60 Years) – Safety Analysis Set (continued)

	Number (%) of Participants					
	After Any Vaccination (N = 240)		After First Vaccination (N = 240)		After Second Vaccination (N = 235)	
	TDV (N = 180)	Placebo (N = 60)	TDV (N = 180)	Placebo (N = 60)	TDV (N = 176)	Placebo (N = 59)
Fever (body temperature in °C)						
N evaluated	179 (99.4)	60 (100)	179 (99.4)	60 (100)	176 (100)	59 (100)
Any	5 (2.8)	4 (6.7)	1 (0.6)	2 (3.3)	4 (2.3)	2 (3.4)
38.0-<38.5	3 (1.7)	3 (5.0)	0	2 (3.3)	3 (1.7)	1 (1.7)
38.5-<39.0	1 (0.6)	1 (1.7)	0	0	1 (0.6)	1 (1.7)
39.0-<39.5	0	0	0	0	0	0
39.5-<40.0	0	0	0	0	0	0
40.0-<40.5	1 (0.6)	0	1 (0.6)	0	0	0
40.5-<41.0	0	0	0	0	0	0
≥41.0	0	0	0	0	0	0

Source: Table 15.3.1.1.2.3.
Pbo: Placebo; TDV: Tetravalent Dengue Vaccine.
Percentages are based on the total number of participants with non-missing data (N evaluated) for each event.
Percentage of N evaluated is based on the number of participants in the Safety Analysis Set who received the specific trial vaccination.
Participants were counted once per AE based on the highest severity category exclusively.
Body temperature ≥38°C (or ≥100.4°F) is defined as fever irrespective of site of measurement.
Solicited systemic AEs summarized in this table occurred within 14 days after vaccination dose.
Records with implausible values are excluded from analysis if they do not fall within the following values: body temperature 32°C to 43°C.
* Fever is excluded from the overall AE count in Table 15.3.1.1.2.3 as no severity grading is applied for it. The totals for '*Any solicited systemic AEs*' row in Table 15.3.1.1.2.4 include participants with fever and therefore do not match the totals in Table 15.3.1.1.2.3.

Table 7 Summary of Solicited Systemic Adverse Events Within 14 Days Postvaccination (Children and Adolescents >4 -< 18 Years) – Safety Analysis Set

	Number (%) of Participants					
	After Any Vaccination (N = 240)		After First Vaccination (N = 240)		After Second Vaccination (N = 238)	
	TDV (N = 180)	Placebo (N = 60)	TDV (N = 180)	Placebo (N = 60)	TDV (N = 179)	Placebo (N = 59)
Any solicited systemic AEs						
N evaluated	179 (99.4)	60 (100)	179 (99.4)	60 (100)	170 (95.0)	59 (100)
Any [a]	20 (11.2)	6 (10.0)	15 (8.4)	4 (6.7)	9 (5.3)	2 (3.4)
Mild	18 (10.1)	6 (10.0)	13 (7.3)	4 (6.7)	9 (5.3)	2 (3.4)
Moderate	2 (1.1)	0	2 (1.1)	0	0	0
Severe	0	0	0	0	0	0
Irritability or Fussiness [b]						
N evaluated	46 (25.6)	14 (23.3)	46 (25.6)	14 (23.3)	38 (21.2)	14 (23.7)
Any	1 (2.2)	1 (7.1)	1 (2.2)	1 (7.1)	0	0
Mild	1 (2.2)	1 (7.1)	1 (2.2)	1 (7.1)	0	0
Moderate	0	0	0	0	0	0
Severe	0	0	0	0	0	0
Drowsiness [b]						
N evaluated	46 (25.6)	14 (23.3)	46 (25.6)	14 (23.3)	38 (21.2)	14 (23.7)
Any	1 (2.2)	2 (14.3)	1 (2.2)	1 (7.1)	1 (2.6)	1 (7.1)
Mild	1 (2.2)	2 (14.3)	1 (2.2)	1 (7.1)	1 (2.6)	1 (7.1)
Moderate	0	0	0	0	0	0
Severe	0	0	0	0	0	0
Loss of Appetite [b]						
N evaluated	46 (25.6)	14 (23.3)	46 (25.6)	14 (23.3)	38 (21.2)	14 (23.7)
Any	0	1 (7.1)	0	0	0	1 (7.1)
Mild	0	1 (7.1)	0	0	0	1 (7.1)
Moderate	0	0	0	0	0	0
Severe	0	0	0	0	0	0
Headache [c]						
N evaluated	133 (73.9)	46 (76.7)	133 (73.9)	46 (76.7)	132 (73.7)	45 (76.3)
Any	8 (6.0)	1 (2.2)	6 (4.5)	1 (2.2)	3 (2.3)	0
Mild	8 (6.0)	1 (2.2)	6 (4.5)	1 (2.2)	3 (2.3)	0
Moderate	0	0	0	0	0	0
Severe	0	0	0	0	0	0

Table 8 Summary of Solicited Systemic Adverse Events Within 14 Days Postvaccination (Children and Adolescents >4 -< 18 Years) – Safety Analysis Set (continued)

	Number (%) of Participants					
	After Any Vaccination (N = 240)		After First Vaccination (N = 240)		After Second Vaccination (N = 238)	
	TDV (N = 180)	Placebo (N = 60)	TDV (N = 180)	Placebo (N = 60)	TDV (N = 179)	Placebo (N = 59)
Asthenia [c]						
N evaluated	133 (73.9)	46 (76.7)	133 (73.9)	46 (76.7)	132 (73.7)	45 (76.3)
Any	10 (7.5)	3 (6.5)	7 (5.3)	2 (4.3)	3 (2.3)	1 (2.2)
Mild	9 (6.8)	3 (6.5)	6 (4.5)	2 (4.3)	3 (2.3)	1 (2.2)
Moderate	1 (0.8)	0	1 (0.8)	0	0	0
Severe	0	0	0	0	0	0
Malaise [c]						
N evaluated	133 (73.9)	46 (76.7)	133 (73.9)	46 (76.7)	132 (73.7)	45 (76.3)
Any	3 (2.3)	0	3 (2.3)	0	0	0
Mild	2 (1.5)	0	2 (1.5)	0	0	0
Moderate	1 (0.8)	0	1 (0.8)	0	0	0
Severe	0	0	0	0	0	0
Myalgia [c]						
N evaluated	133 (73.9)	46 (76.7)	133 (73.9)	46 (76.7)	132 (73.7)	45 (76.3)
Any	7 (5.3)	2 (4.3)	5 (3.8)	1 (2.2)	3 (2.3)	1 (2.2)
Mild	6 (4.5)	2 (4.3)	4 (3.0)	1 (2.2)	3 (2.3)	1 (2.2)
Moderate	1 (0.8)	0	1 (0.8)	0	0	0
Severe	0	0	0	0	0	0
Fever (body temperature in °C)						
N evaluated	179 (99.4)	60 (100)	179 (99.4)	60 (100)	178 (99.4)	59 (100)
Any	5 (2.8)	1 (1.7)	2 (1.1)	1 (1.7)	3 (1.7)	1 (1.7)
38.0-<38.5	3 (1.7)	0	1 (0.6)	0	2 (1.1)	0
38.5-<39.0	0	0	0	0	0	1 (1.7)
39.0-<39.5	0	1 (1.7)	0	1 (1.7)	0	0
39.5-<40.0	0	0	0	0	0	0
40.0-<40.5	2 (1.1)	0	1 (0.6)	0	1 (0.6)	0
40.5-<41.0	0	0	0	0	0	0
≥41.0	0	0	0	0	0	0

Source: Table 15.3.1.1.2.3.
TDV: Tetravalent Dengue Vaccine.
Percentages are based on the total number of participants with non-missing data (N evaluated) for each event.
Percentage of N evaluated is based on the number of participants in the Safety Analysis Set who received the specific trial vaccination.

There were no prolonged solicited systemic AEs

Unsolicited Adverse Events within 28 days

Nineteen (5.3%) TDV recipients and 6 (5.0%) placebo recipients experienced unsolicited AEs of vaccination. The percentage of participant reporting vaccine related unsolicited AEs 28 days after any vaccination was 1.4% in the TDV group and 0% in the placebo group.

Table 9 Investigational Product-Related Unsolicited Adverse Events Up to 28 Days Post-Vaccination by System Organ Class and Preferzed Term Safety Analysis SeT After Any Vaccination; Age group (Cohort 1 and Cohort 2 combined) : >4 to <= 60 years

	TDV (N=360)		Placebo (N=120)		Total (N=480)	
System Organ Class Preferred Term	No. of Events	Subjects n(%)	No. of Events	Subjects n(%)	No. of Events	Subjects n(%)
Any Adverse Events	8	5 (1.4)	0	0 (0.0)	8	5 (1.0)
General disorders and administration site conditions	3	3 (0.8)	0	0 (0.0)	3	3 (0.6)
Influenza like illness	3	3 (0.8)	0	0 (0.0)	3	3 (0.6)
Respiratory, thoracic and mediastinal disorders	3	1 (0.3)	0	0 (0.0)	3	1 (0.2)
Nasal congestion	1	1 (0.3)	0	0 (0.0)	1	1 (0.2)
Oropharyngeal pain	1	1 (0.3)	0	0 (0.0)	1	1 (0.2)
Sneezing	1	1 (0.3)	0	0 (0.0)	1	1 (0.2)
Skin and subcutaneous tissue disorders	2	1 (0.3)	0	0 (0.0)	2	1 (0.2)
Rash	2	1 (0.3)	0	0 (0.0)	2	1 (0.2)

The percentage of adults who experienced unsolicited AEs 28 days after any vaccination was 3.9% and 5.0% in the TDV and placebo groups, respectively. The percentage of adults reporting vaccine related unsolicited AEs 28 days after any vaccination was 1.1% in the TDV group and 0% in the placebo group.

The percentage of children and adolescents reporting unsolicited AEs 28 days after any, vaccination was 6.7% and 5.0% in the TDV and placebo groups, respectively. The percentage of children and adolescents reporting vaccine related unsolicited AEs 28 days after any vaccination was 1.7% in the TDV group and 0% in the placebo group

All unsolicited AEs were mild or moderate except for 1 adult participant who experienced severe, unrelated headache, lasting 6 days, which was resolved. All participants recovered from their non related AEs except for 2 participants who recovered from hyperbilirubinemia and hypertension, respectively, at the time of the last safety data collection.

MAAEs

60 (12.5%) participants reported MAAEs during the trial. Of these, 46 (12.8%) were from the TDV group and 14 (11.7%) were from the placebo group. Most MAAEs were mild (53 [11.0%]) or moderate (6 [1.3%]) and none of the MAAEs was considered related to TDV or placebo or to trial procedures.

The percentage of MAAEs after any vaccination was 11.1% in the TDV group and 6.7% in placebo group after any vaccination for adults. A single adult TDV recipient experienced the severe, non-serious and un-related MAAE of headache on Day 22 after the first vaccination. Moreover, a single adult participant experienced a MAAE that led to discontinuation from TDV as well as discontinuation from the trial. This event occurred after the first TVD dose, on Day 2, and consisted of a moderate pharyngitis assessed as unrelated to TDV or trial procedures.

The percentage of MAAEs after any vaccination was 14.4% in the TDV group and 16.7% in the placebo group for children and adolescents. MAAEs experienced by children and adolescents were either mild or moderate in intensity

Deaths, Other Serious Adverse Events, and Other Significant Adverse Events

There were no deaths, no SAEs and no other important medical events or other significant AEs.

2.3.3. Discussion on clinical aspects

In this submission Takeda presented the results from Trail DEN-302 according to Article 46 of the EU Paediatric Regulation. Trial DEN 302 was a phase 3, randomized, multi-center, double-blind, placebo-controlled trial to evaluate the safety and immunogenicity of a 2-dose schedule of TDV administered by SC injection in healthy participants aged 4 to 60 years in India.

Immunogenicity

A total of 480 participants were enrolled and randomized in parallel in 2 cohorts (240 adults ≥18-≤60 years of age and 240 children and adolescents ≥4-<18 years of age).

Participants were randomly assigned 3:1, to receive TDV or placebo on Day 1 and the second dose of TDV or placebo 3 months later. Of these, 180 participants in each cohort received TDV (360 participants in total), and 60 participants in each cohort received placebo (120 participants in total).

Primary and secondary objectives were both related to safety and immunogenicity and are considered to be adequate for the aim of the trial, which was to confirm the clinical data of the vaccine in indian population.

Overall, the design of the trial and the analysed populations are endorsed.

Most of the trial participants (97.9% in cohort 1 and 99.2% in cohort 2) received 2 doses of treatment (TDV or placebo) and more than 97% completed the trial.

Regarding demographic and baseline characteristics of the trial participants, there are some imbalances that are worth mentioning. In the overall trial population, there were 63.3% of males, and this imbalance was particularly evident in the adult cohort (≥18-≤60 years of age) in which 71.7% of the participants were male. The MAH explained that this was due to an open enrolment policy, and that adult male overvolunteering is frequent in India. This is not expected to have a serious impact in the immunogenicity results.

Moreover, 91.5% of the overall trial participants were dengue seropositive at baseline and 79.6% were seropositive to all four dengue serotypes, these numbers were higher in adults than in children, as expected.

Immunogenicity is measured by a dengue MNT assay performed by a single laboratory, and this is endorsed.

Immunogenicity results are in line with what TDV vaccine has shown in the trials assessed for the MAA. TDV elicited a strong immune response in adults, adolescents and children at D120 for the four dengue serotypes.

In all the immunogenicity results data it is observed that the number of participants that have been evaluated at the different time points are different, there are more participants assessed at D1 than at D120 or D270, and this is expected, but it is observed that the number of measures in D120 is consistently lower than at D1 (this could be expected) and lower than at D270. The MAH explained that this was due to the fact that D120 time window was narrower (8 days as opposed to 22), as it was the time point for the primary immunogenicity endpoint.

The fact that there are so few seronegative participants, precludes drawing any conclusions from this study in that population. Taking into account that the study was carried out in different locations in order to recruit a representative sample of the Indian population, this does not pose a problem for the objectives of this study.

Safety

In this submission Takeda presented the results from Trail DEN-302 according to Article 46 of the EU Paediatric Regulation. Trial DEN 302 was a phase 3, randomized, multi-center, double-blind, placebo-controlled trial to evaluate the safety and immunogenicity of a 2-dose schedule of TDV administered by SC injection in healthy participants aged 4 to 60 years in India. The primary objectives were to assess the safety profile of TDV administered as 2 doses given 3 months apart in healthy adults, adolescents, and children.

The Safety Analysis Set consisted of all participants who received at least 1 dose of TDV or placebo. Specifically, a total of 480 participants were enrolled and randomized in parallel in 2 cohorts: (i) Cohort 1 (adults ≥18-≤60 years of age): 240 adults were enrolled and randomly assigned (3:1) to receive either TDV (N = 180) or placebo (N = 60) and (ii) Cohort 2 (children and adolescents ≥4-<18 years of

age): 240 children and adolescents were enrolled and randomly assigned (3:1) to receive either TDV (N = 180) or placebo (N = 60).

The demographic and baseline characteristics in safety analysis were generally similar between TDV and placebo. However higher percentage of male (63.3%) than female (36.7%) was enrolled in the trail DEN-302 and this difference was observed more in adults (male:71.7% vs female:28.3%) than in children and adolescents (male:55.0% vs female:45.0%). As it is known, according to the data of Placebo-Controlled Safety Pool in the initial MA, the incidences of solicited and unsolicited AEs in male and female subjects after Qdenga followed the pattern observed in the overall target population. However, solicited AEs, including AEs within 30 minutes and prolonged solicited AEs, and unsolicited AEs were more commonly experienced by female subjects. Therefore, the reactogenicity data reported in this study DEN-302 could be underreported based on a lower presence of female participants.

In addition, 91.5% of the overall trial participants were dengue seropositive at baseline. According to the data in the initial MA, overall solicited AEs, including AEs within 30 minutes and prolonged solicited AEs, and unsolicited AEs in TDV were more frequently reported in seronegative than in seropositive. Therefore, the reactogenicity data reported in this study DEN-302 could be underreported based on lower presence of seronegative participants.

All AEs within the 30 minutes after any vaccination reported in participants ≥4 to ≤60 years were local, no systemic AEs within 30 minutes were reported in the trail. The frequency was slightly higher in TDV group (11.4%) than in placebo (8.3%) and it was observed only after the first dose. The principal local solicited AEs within 30 minutes after any vaccine administration was injection site pain.

Slightly higher frequencies of solicited local AEs after any vaccination were reported in TDV group (20,4%) than in placebo (17.5%). All solicited local AEs reported were mild-moderate in severity. No difference in frequency was observed when comparing first and second dose of TDV. However fewer local AEs were reported after the second vaccination than after the first administration of placebo. No difference related to age were observed regarding solicited local AEs.

No difference regarding solicited systemic AEs frequency after any vaccination was observed between TDV and placebo groups (13.7% and 12.5%, respectively). Most of them were considered related (11.2% in TDV group and 11.7% in placebo group) with mild-moderate severity. Fewer systemic AEs were reported after the second vaccination than after the first vaccination and lower frequency was observed in children and adolescents than in adults' participants in both vaccination groups.

Although the incidence of fever was not reported from the pool of the cohorts (aged 4 to 60 years), the frequency of fever across the 3 age intervals (≥4-<6 years,≥6-<18 years, ≥18-≤60 years) were 0%, 3,8% and 2,8% in TDV group and 0%, 2,2% and 6,7% in placebo respectively.There were 3 events of fever considered as severe (≥40°) in TDV group (2 events in ≥6-<18 years group and one event in ≥18-≤60 years group) and none in placebo group.

No difference was observed regarding the incidence of unsolicited AEs between groups. The frequency of unsolicited AEs considered related was very low in TDV and placebo group (1.1% in the TDV group and 0% in placebo). No new safety signal was observed regarding unsolicited AEs within 28 days after vaccination.

The incidence of MAAES during the study was low and similar between groups (12.8% in TDV group and 11.7% in placebo group). None was considered related to TDV or placebo or to trial procedures. Comparing the incidence by age, higher percentage was observed in children and adolescents (14.4% and 16.7%, respectively) than in adults (11.1% and 6.7%, respectively).

There were no deaths, no SAEs and no other important medical events or other significant AEs.

Conclusion

Immunogenicity conclusion

Overall, the results that this study contributes are in line with previous results from the clinical studies already assessed in the MAA and therefore it is not recommended to update the Product Information. Additionally, the results from study DEN-302 do not change the B/R balance, which remains positive.

Safety conclusion

The overall safety pattern observed in this trail DEN-302 was similar to the known safety profile of Qdenga (even with lower reactogenicity) and no new safety sign was observed.

However, the incidence of solicited AEs (including local and systemic AEs) and unsolicited AEs, observed in the trial DEN-302, were lower than the observed in previous trials (specifically in Placebo-Controlled Safety Pool in initial MA). This difference could be explained, but not only, by the higher percentage of male and dengue seropositive at baseline participants enrolled in DEN-302, since reactogenicity is known, according to the data of Placebo-Controlled Safety Pool in initial MA, to be higher in female and seronegatives than in male and seropositives at baseline. In addition, it is expected that the difference of percentage of race of Asian participants in DEN-302 (100%) compared to Placebo-Controlled Safety Pool (42% aprox) could also contribute to the observed difference in incidence.

3. Rapporteur's overall conclusion and recommendation

The data presented in this submission are in line with the data which were assessed in the Qdenga MAA and therefore there is no change in the B/R balance nor there is any requirement to update the Product Information. The MAH provided satisfactory responses to the RSI.

☒ **Fulfilled:**

No regulatory action required.

4. Request for supplementary information

Based on the data submitted, the MAH should address the following questions as part of this procedure:

Question 1

Question 2

In the demographic data for the study participants, it is noticeable that male participants are substantially more represented than females. This was specially outstanding in the older participants (71,7% males in subjects ≥18-<60 years of age). Although it is not expected that this imbalance has important effects in the immunogenicity results, a justification should be provided.

Question 3

It is observed that the number of measures in D120 is consistently lower than at D1 (this could be expected) and lower than at D270. This should be adequately justified.

The timetable is a 30-day response timetable with clock stop.

5. Assessment of the responses to the request for supplementary information

Question 1

The issue is solved.

Question 2

In the demographic data for the study participants, it is noticeable that male participants are substantially more represented than females. This was specially outstanding in the older participants (71,7% males in subjects ≥18-<60 years of age). Although it is not expected that this imbalance has important effects in the immunogenicity results, a justification should be provided.

Summary of the MAH's response

Trial DEN-302 protocol design did not stipulate any restrictions to enrolment bias of one gender over the other. Nor were the trial centres influenced towards skewed enrolment of any one gender. The observed enrolment in Trial DEN-302, therefore, was based on a policy of open enrolment to any individual who volunteered to participate willingly at any of the 10 trial centres in this trial.

The MAH notes that disproportionately higher enrolment of adult male participants appears to be a frequent trend with vaccine trials conducted in India, as evidenced from other examples of trials [1-5]. On the other hand, unrestricted enrolment employed in Trial DEN-302 is better reflected in the balance observed with the paediatric cohort of this trial: 55% male and 45% female participants (DEN-302 CSR, Table 10.d).

Assessment of the MAH's response

The MAH explains that the sex imbalance was due to an open enrolment policy, which accepted any volunteering individual. The MAH also provides evidence in the literature that adult male overvolunteering is frequent in India.

The issue is solved.

Question 3

It is observed that the number of measures in D120 is consistently lower than at D1 (this could be expected) and lower than at D270. This should be adequately justified.

Summary of the MAH's response

Blood samples for serological immunogenicity testing (MNT) were collected from all participants before vaccination at Day 1 (Month 0 [M0]), 1 month post second vaccination at Day 120 (M4), and at the end of trial (Day 270 [M9] or earlier for early terminations). The blood sample obtained at Day 120 (M4) was to be taken at least 28 days after the second (Day 90 [M3]) TDV or placebo vaccination. Table 9.c of DEN-302 CSR, presents the overview of the trial procedures and the related time window.

The number of participants with available data differs across time points because each visit has a different pre-defined assessment window. Per Table 9.b of the Statistical Analysis Plan (SAP), the per-protocol set (PPS) analysis visit window for Day 120 analyses was 8 days (-1/+7). Participant visits outside this window were therefore excluded from the Day 120 PPS analyses.

By contrast, the PPS analysis visit window for Day 270 was wider (22 days [-7/+14]) (DEN-302 CSR, Table 9.c), as compared to Day 120. There were more participant data within this wider window for Day 270 than for Day 120 and therefore more evaluable observations at Day 270.

The difference in windows between two timepoints is because, at Day 120, the blood sample for the primary endpoint was collected. For this endpoint, a narrow time window was chosen to help minimize variability around the peak immune response and support comparability across participants.

Additionally, when considering the full analysis set (FAS) Day 120 analysis, which applies a much wider window (104 days [-28/+75]), the number of evaluable observations is comparable to that at Day 1.

Taken together this explains the observation of fewer numbers of participant data observed in the Day 120 analyses as compared with the Day 270 analyses.

Assessment of the MAH's response

The MAH explains that the fact that there are more evaluable samples at D270 than at D120 is due to the different visit window width (8 days for D120, 22 days for D270). The time window was narrower at D120 as these were the samples used for the primary immunogenicity endpoint.

The issue is solved.