VACCINES

TAK-003 (Tetravalent Dengue Vaccine Candidate)

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Disclaimers

- TAK-003 is an investigational compound that has not been approved for use by the US Food and Drug Administration
- There is no guarantee TAK-003 will be approved in any country or countries for use in indications under investigation in the trials or studies discussed herein
- Regulatory approval and use of TAK-003 is dependent on review by relevant local authorities
  - Currently, TAK-003 is approved for use in Indonesia, the EU, and UK

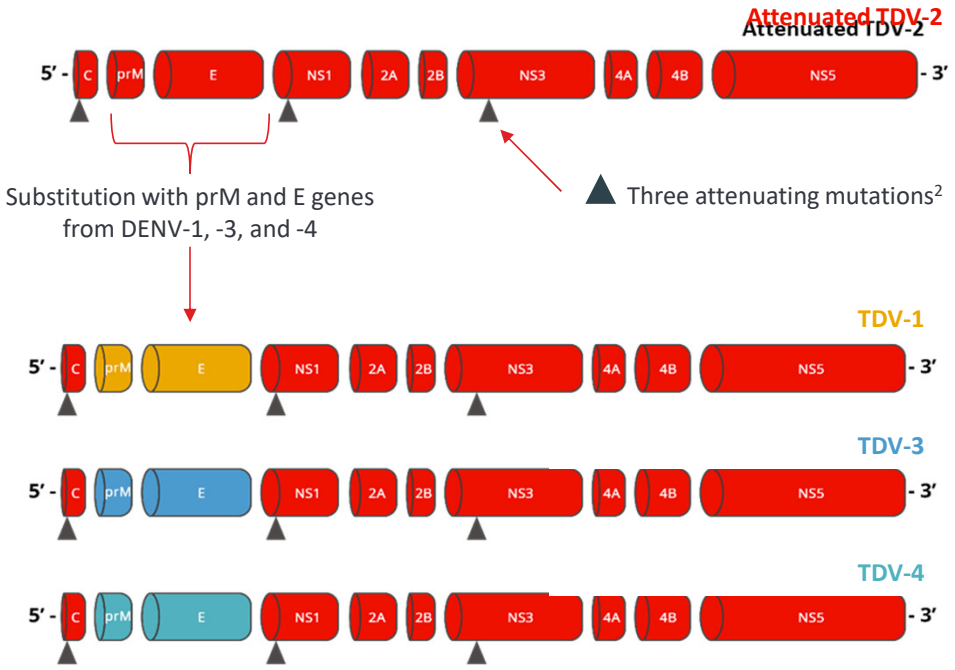
ACIP, Advisory Committee on Immunization Practices.

Topics to be covered

- Construct of the vaccine
- Immune response profile
- Overview of the clinical development
- Efficacy profile from the pivotal efficacy trial
- Safety profile from an integrated analysis of placebo-controlled trials
- Immunogenicity data from the pivotal efficacy trial
- Summary

TAK-003 is based on a live, attenuated DENV-2 virus backbone expressing E and prM proteins of all four DENV serotypes

Genetic structure and design of TAK-003[1–3]



C, capsid; DENV, dengue virus; E, envelope; NS, non-structural; prM, pre-membrane; TDV, tetravalent dengue vaccine.

1. Osorio JE, et al. *Expert Rev Vaccines* 2016;15:497–508; 2. Osorio JE, et al. *Vaccine* 2015;33:7112–7120; 3. Patel SS, et al. *Clin Infect Dis* 2022. doi:10.1093/cid/ciac418 [Epub ahead of print].

In clinical trials, TAK-003 activated multiple facets of immunity

Humoral-mediated immunity

- TAK-003 elicited neutralizing antibodies against each of DENV-1,-2,-3,-4[1,2]
- TAK-003 elicited cross-reactive antibodies that blocked the activity of DENV NS1 protein[3]
- TAK-003 elicited type-specific memory B cells that target DENV-1, -2, -3, -4*[4]

Cell-mediated immunity

- TAK-003 stimulated cross-reactive CD4+ and CD8+ T-cell responses[5]

Innate immunity

- TAK-003 stimulated production of T cells capable of producing IFNγ, TNFα, and IL-2[5]

A broad spectrum of immune responses may contribute to protection against infection, virus clearance, and prevention of severe disease[1–5]

*These data were gathered from non-human primates and humans.
CD, cluster of differentiation; DENV, dengue virus; IFN, interferon; IL, interleukin; NS, non-structural; TNF, tumor necrosis factor.
1. Biswal S, et al. *Lancet* 2020;395:1423–1433; 2. Tricou V, et al. *Lancet* 2020;395:1434–1443; 3. Sharma M, et al. *J Infect Dis* 2020;221:867–877; 4. Michlmayr D, et al. *J Infect Dis* 2021;233:247–257; 5. Tricou V, et al. *Vaccine* 2022;40:1143–1151.

Overview of the clinical development program

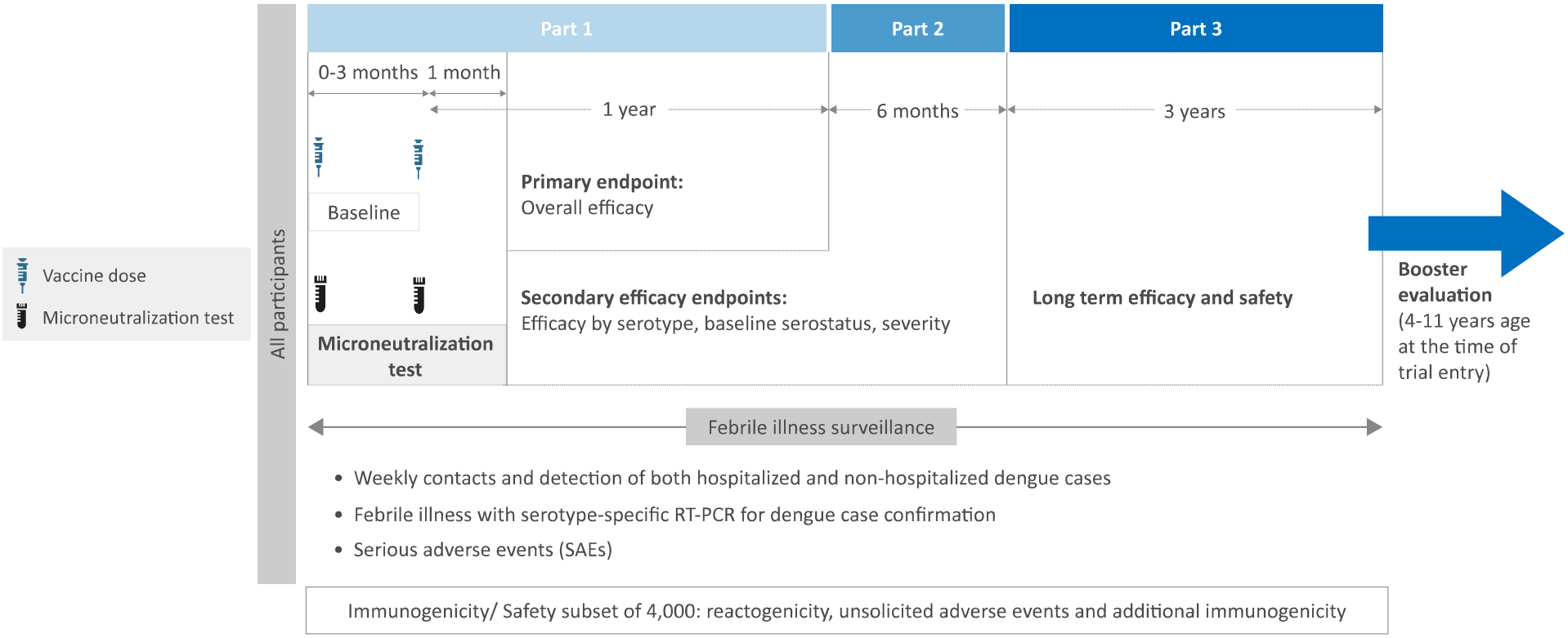
- 19 clinical trials conducted in 13 dengue endemic and non-endemic countries
- Over 28,000 children/adults (aged 1.5–60 years) participated in Phase I–III clinical studies
- Clinical development included both baseline seronegative and seropositive participants
- ~20,000 participants received at least one dose of TAK-003

Ab, antibody; CMI, cell-mediated immunity; HepA, hepatitis A; HPV9, human papillomavirus 9 vaccine; S&I, safety and immunogenicity.

1. ClinicalTrials.gov NCT01110551. Available at: https://www.clinicaltrials.gov/ct2/show/NCT01110551 (accessed January 2023); 2. ClinicalTrials.gov NCT01224639. Available at: https://www.clinicaltrials.gov/ct2/show/NCT01224639 (accessed January 2023); 3. ClinicalTrials.gov NCT01765426. Available at: https://www.clinicaltrials.gov/ct2/show/NCT01765426 (accessed January 2023); 4. ClinicalTrials.gov NCT01542632. Available at: https://www.clinicaltrials.gov/ct2/show/NCT01542632 (accessed January 2023); 5. ClinicalTrials.gov NCT01728792. Available at: https://www.clinicaltrials.gov/ct2/show/NCT01728792 (accessed January 2023); 6. ClinicalTrials.gov NCT02193087. Available at: https://www.clinicaltrials.gov/ct2/show/NCT02193087 (accessed January 2023); 7. ClinicalTrials.gov NCT01511250. Available at: https://www.clinicaltrials.gov/ct2/show/NCT01511250 (accessed January 2023); 8. ClinicalTrials.gov NCT02302066. Available at: https://www.clinicaltrials.gov/ct2/show/NCT02302066 (accessed January 2023); 9. ClinicalTrials.gov NCT02425098. Available at: https://www.clinicaltrials.gov/ct2/show/NCT02425098 (accessed January 2023); 10. ClinicalTrials.gov NCT02747927. Available at: https://www.clinicaltrials.gov/ct2/show/NCT02747927 (accessed January 2023); 11. ClinicalTrials.gov NCT02948829. Available at: https://www.clinicaltrials.gov/ct2/show/NCT02948829 (accessed January 2023); 12. ClinicalTrials.gov NCT03999996. Available at: https://www.clinicaltrials.gov/ct2/show/NCT03999996 (accessed January 2023); 13. ClinicalTrials.gov NCT03423173. Available at: https://www.clinicaltrials.gov/ct2/show/NCT03423173 (accessed January 2023); 14. ClinicalTrials.gov NCT03341637. Available at: https://www.clinicaltrials.gov/ct2/show/NCT03341637 (accessed January 2023); 15. ClinicalTrials.gov NCT03771963. Available at: https://www.clinicaltrials.gov/ct2/show/NCT03771963 (accessed January 2023); 16. ClinicalTrials.gov NCT03746015. Available at: https://www.clinicaltrials.gov/ct2/show/NCT03746015 (accessed January 2023); 17. ClinicalTrials.gov NCT03342898. Available at: https://www.clinicaltrials.gov/ct2/show/NCT03342898 (accessed January 2023); 18. ClinicalTrials.gov NCT03525119. Available at: https://www.clinicaltrials.gov/ct2/show/NCT03525119 (accessed January 2023); 19. ClinicalTrials.gov NCT04313244. Available at: https://www.clinicaltrials.gov/ct2/show/NCT04313244 (accessed January 2023).

TIDES (DEN-301): Pivotal Phase III trial design

20,071 children (aged 4–16 years) received either TAK-003 or placebo in a 2:1 ratio[1,2]



RT-PCR, reverse transcriptase polymerase chain reaction; SAE, serious adverse event.

1. ClinicalTrials.gov NCT02747927. Available at: https://clinicaltrials.gov/ct2/show/NCT02747927 (accessed January 2023); 2. Biswal S, et al. *N Engl J Med* 2019;281:2009–2019.

Demographic and baseline characteristics: Safety set

Characteristic	Placebo n 6687	TAK 003 n 13,380
Seronegative, n (%)	1832 (27.4)	3714 (27.8)
Mean age, years (SD)	9.6 (3.34)	9.6 (3.36)
4–5 years, n (%)	846 (12.7)	1702 (12.7)
6–11 years, n (%)	3697 (55.3)	7387 (55.2)
12–16 years, n (%)	2144 (32.1)	4291 (32.1)
Asia, n (%)	2993 (44.8)	5996 (44.8)
Latin America, n (%)	3694 (55.2)	7384 (55.2)

Baseline serostatus data were available for 6684 and 13,375 safety set participants in the placebo and TAK-003 groups, respectively.
n refers to number of participants in the safety analysis set.
Seronegative at baseline: seronegative to all four DENV serotypes. Seropositive at baseline: reciprocal neutralizing titer ≥10 for one or more DENV serotypes.
DENV, dengue virus; SD, standard deviation.
Takeda. Data on file.

Trial sites and background dengue cases in the placebo group

Up to 57 months post 1st dose: Safety set[1]

APAC, Asia-Pacific; DENV, dengue virus; LATAM, Latin America; VCD, virologically confirmed dengue.

1. 1. Tricou V, et al. Efficacy and safety of Takeda's tetravalent dengue vaccine candidate (TAK-003) after 4.5 years of follow-up. Presented at NECTM, Rotterdam, Netherlands, 8–10 June 2022; 2. Takeda. Data on File.

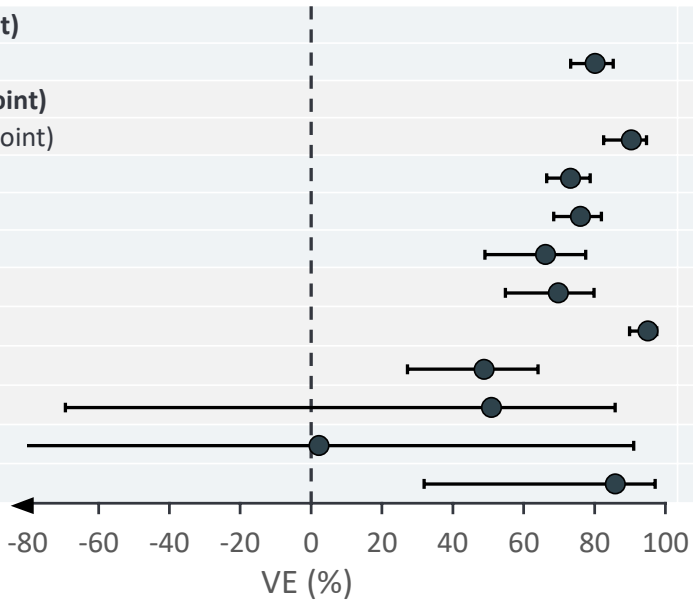
Primary and secondary efficacy endpoint analysis

Vaccine efficacy = 1 – hazard ratio (TAK-003 vs. placebo). Hazard ratio estimated from Cox proportional hazards model with adjustment for age and stratified by region.

DEN-301: Primary and secondary endpoints

Primary and secondary endpoints per protocol set data; placebo to TAK-003 1:2 randomization[1–3]

Endpoint	VCD (per 100 person-years) Placebo n=6317	TAK-003 n=12,704	VE	95% CI
30 days to 12 months post 2nd dose (primary endpoint)				
VCD by any serotype	149 (2.6)	61 (0.5)	**80.2**	(73.3, 85.3)
30 days to 18 months post 2nd dose (secondary endpoint)				
VCD leading to hospitalization (key secondary endpoint)	66 (0.8)	13 (<0.1)	**90.4**	(82.6, 94.7)
VCD by any serotype	206 (2.4)	114 (0.6)	**73.3**	(66.5, 78.8)
Baseline seropositive	150 (2.4)	75 (0.6)	**76.1**	(68.5, 81.9)
Baseline seronegative	56 (2.4)	39 (0.8)	**66.2**	(49.1, 77.5)
VCD by DENV-1	62 (0.7)	38 (0.2)	**69.8**	(54.8, 79.9)
VCD by DENV-2	80 (0.9)	8 (<0.1)	**95.1**	(89.9, 97.6)
VCD by DENV-3	60 (0.7)	63 (0.4)	**48.9**	(27.2, 64.1)
VCD by DENV-4	5 (<0.1)	5 (<0.1)	**51.0**	(−69.4, 85.8)
DCAC-defined severe VCD	1 (<0.1)	2 (<0.1)	**2.3**	(−997.5, 91.1)
DHF	7 (<0.1)	2 (<0.1)	**85.9**	(31.9, 97.1)

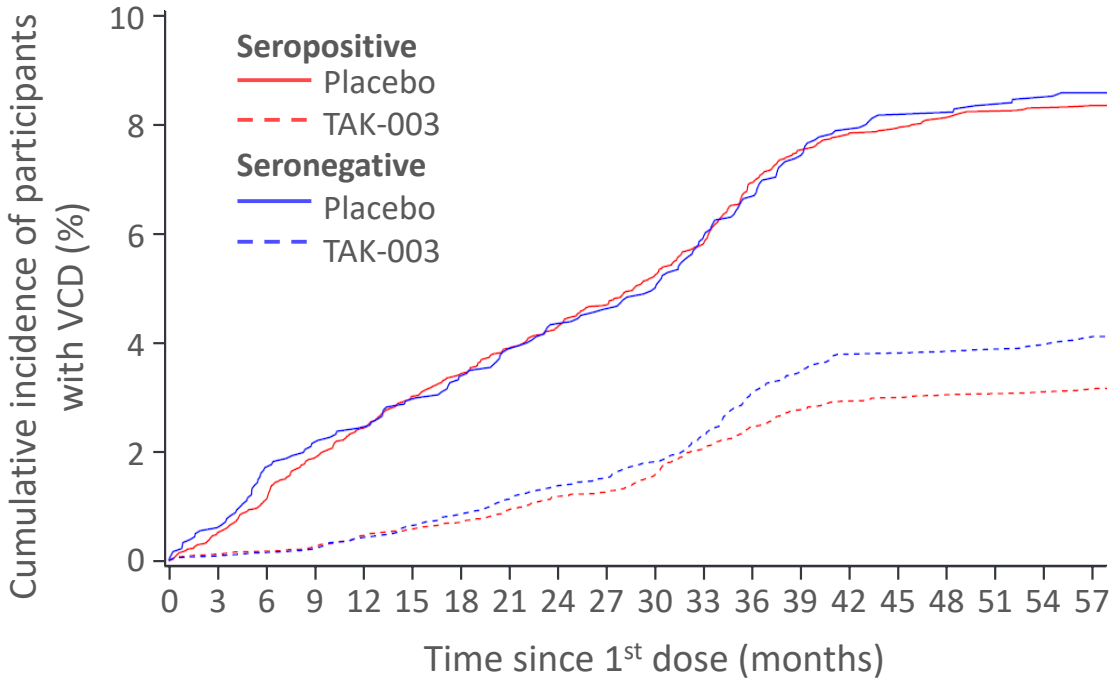


VE against VCD by any serotype in the 30 days to 18 months post 2nd dose time frame was an exploratory endpoint;
Seronegative at baseline: seronegative to all four DENV serotypes; seropositive at baseline: reciprocal neutralizing titer ≥10 for one or more DENV serotypes.
CI, confidence interval; DCAC, Dengue Case Adjudication Committee; DENV, dengue virus; DHF, dengue hemorrhagic fever; VCD, virologically confirmed dengue; VE, vaccine efficacy.
1. Biswal S, et al. *Lancet* 2020;395:1423–1433; 2. Biswal S, et al. *N Engl J Med* 2019;381:2009–2019; 3. Takeda. Data on File.

Cumulative efficacy results over ~57 months (safety set data)

Vaccine efficacy = 1 – hazard ratio (TAK-003 vs. placebo). Hazard ratio estimated from Cox proportional hazards model with adjustment for age and stratified by region.

TAK-003 was efficacious against VCD over 57 months regardless of baseline serostatus



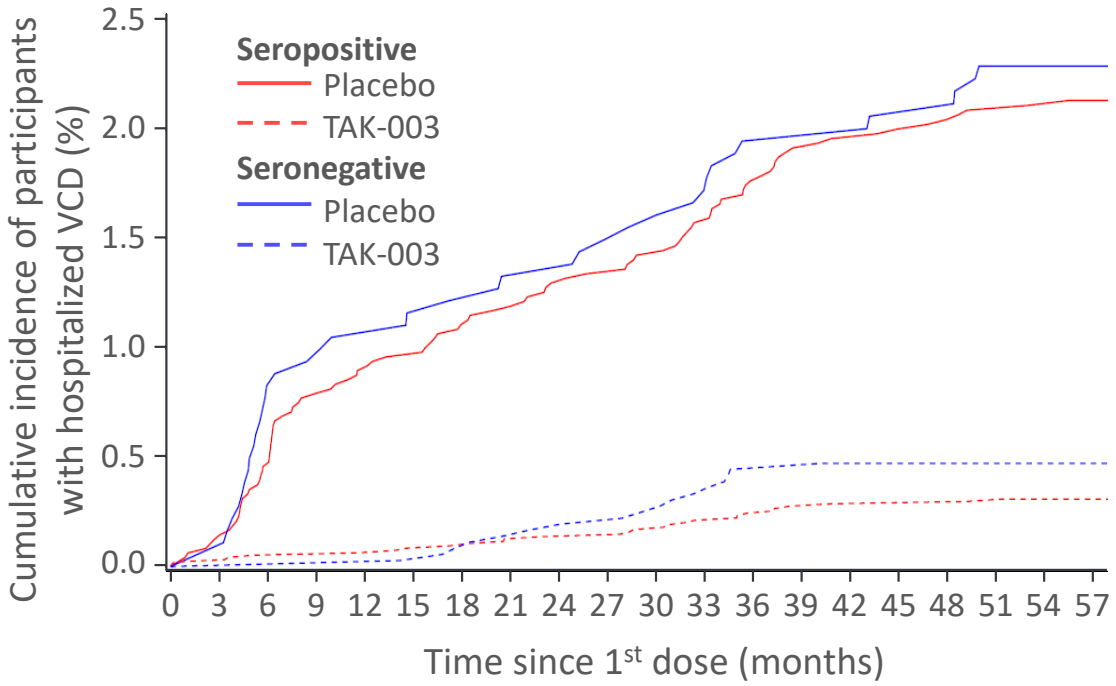
Cumulative safety data set[1]

	VE (95% CI)
Overall	**61.2** (56.0, 65.8)
Seronegative	**53.5** (41.6, 62.9)
Seropositive	**64.2** (58.4, 69.2)

Safety set data truncated at 57 months post 1st dose. Seronegative at baseline: seronegative to all four DENV serotypes; seropositive at baseline: reciprocal neutralizing titer ≥10 for one or more DENV serotypes.
CI, confidence interval; DENV, dengue virus; VCD, virologically confirmed dengue.

1. Tricou V, et al. Efficacy and safety of Takeda's tetravalent dengue vaccine candidate (TAK-003) after 4.5 years of follow-up. Presented at NECTM, Rotterdam, Netherlands, 8–10 June 2022.

TAK-003 was efficacious against hospitalized VCD over 57 months regardless of baseline serostatus



Cumulative safety data set[1]

	VE (95% CI)
Overall	**84.1** (77.8, 88.6)
Seronegative	**79.3** (63.5, 88.2)
Seropositive	**85.9** (78.7, 90.7)

Safety set data truncated at 57 months post 1st dose. Seronegative at baseline: seronegative to all four DENV serotypes; seropositive at baseline: reciprocal neutralizing titer ≥10 for one or more DENV serotypes.
CI, confidence interval; DENV, dengue virus; VCD, virologically confirmed dengue.

1. Tricou V, et al. Efficacy and safety of Takeda's tetravalent dengue vaccine candidate (TAK-003) after 4.5 years of follow-up. Presented at NECTM, Rotterdam, Netherlands, 8–10 June 2022.

Efficacy against VCD: By baseline serostatus and serotype

1st dose to end of Part 3: Safety set (~57 months)[1,2]

	Placebo n 6687	TAK 003 n 13,380	VE (95% CI)
VCD, n (per 100 person-years)			
Seropositive			
DENV-1	151 (0.7)	133 (0.3)	**56.1** (44.6, 65.2)
DENV-2	135 (0.6)	54 (0.1)	**80.4** (73.1, 85.7)
DENV-3	97 (0.4)	96 (0.2)	**52.3** (36.7, 64.0)
DENV-4	20 (<0.1)	12 (<0.1)	**70.6** (39.9, 85.6)
Seronegative			
DENV-1	79 (1.0)	89 (0.5)	**45.4** (26.1, 59.7)
DENV-2	58 (0.7)	14 (<0.1)	**88.1** (78.6, 93.3)
DENV-3	16 (0.2)	36 (0.2)	**−15.5** (−108.2, 35.9)
DENV-4	3 (<0.1)	12 (<0.1)	**−105.6** (−628.7, 42.0)

n refers to number of participants in the safety set. Numbers of VCD (per 100 person-years) are based on the number of participants evaluated.
Repeat episodes of VCD were excluded from efficacy analysis at VCD or serotype level as applicable.
Seronegative at baseline: seronegative to all four DENV serotypes. Seropositive at baseline: reciprocal neutralizing titer ≥10 for one or more DENV serotypes.
CI, confidence interval; DENV, dengue virus; VCD, virologically confirmed dengue; VE, vaccine efficacy.
1. Tricou V, et al. Efficacy and safety of Takeda's tetravalent dengue vaccine candidate (TAK-003) after 4.5 years of follow-up. Presented at NECTM, Rotterdam, Netherlands, 8–10 June 2022; 2. Takeda. Data on File.

Efficacy against hospitalized VCD: By baseline serostatus and serotype

1st dose to end of Part 3: Safety set (~57 months)[1,2]

	Placebo n 6687	TAK 003 n 13,380	VE (95% CI)
Hospitalized VCD, n (per 100 person-years)			
Seropositive			
DENV-1	24 (0.1)	16 (<0.1)	**66.8** (37.4, 82.3)
DENV-2	59 (0.3)	5 (<0.1)	**95.8** (89.6, 98.3)
DENV-3	15 (<0.1)	8 (<0.1)	**74.0** (38.6, 89.0)
DENV-4	3 (<0.1)	0 (0.0)	**100** (NE, NE)
Seronegative			
DENV-1	14 (0.2)	6 (<0.1)	**78.4** (43.9, 91.7)
DENV-2	23 (0.3)	0 (0.0)	**100** (NE, NE)
DENV-3	3 (<0.1)	11 (<0.1)	**−87.9** (−573.4, 47.6)
DENV-4	1 (<0.1)	0 (0.0)	**100** (NE, NE)

Rate of hospitalization among VCD cases in placebo group: The Philippines, 17/191 (**8.9%**); Sri Lanka, 70/103 (**68.0%**); Thailand, 25/64 (**39.1%**); Brazil, 2/24 (**8.3%**); Colombia, 14/87 (**16.1%**); Dominican Republic, 4/22 (**18.2%**); Nicaragua, 8/24 (**33.3%**); Panama, 2/45 (**4.4%**).

n refers to number of participants in the safety set. Numbers of hospitalized VCD (per 100 person-years) are based on the number of participants evaluated.

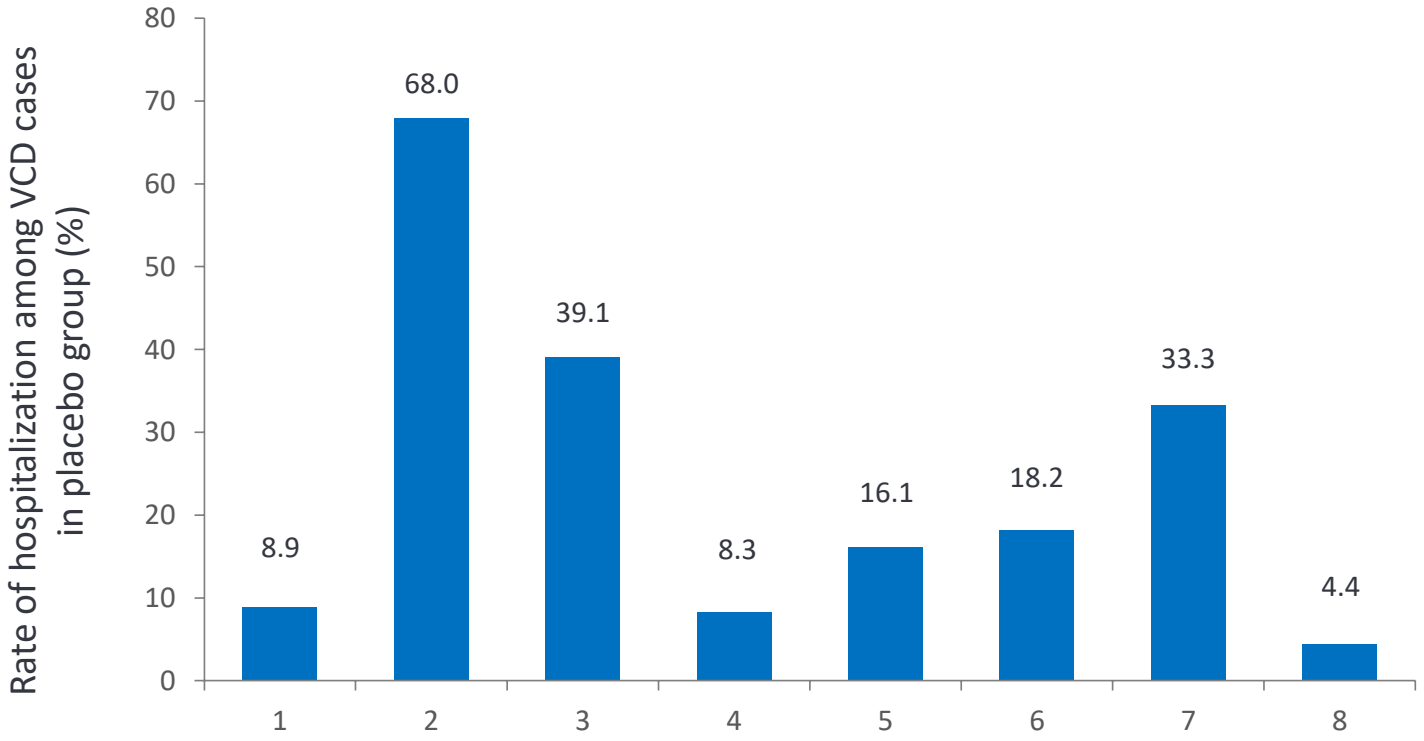
Seronegative at baseline: seronegative to all four DENV serotypes. Seropositive at baseline: reciprocal neutralizing titer ≥10 for one or more DENV serotypes.

CI, confidence interval; DENV, dengue virus; NE, non-estimable; VCD, virologically confirmed dengue; VE, vaccine efficacy.

1. Tricou V, et al. Efficacy and safety of Takeda's tetravalent dengue vaccine candidate (TAK-003) after 4.5 years of follow-up. Presented at NECTM, Rotterdam, Netherlands, 8–10 June 2022; 2. Takeda. Data on File.

Rate of hospitalization among VCD cases by country

Placebo group analysis 1st dose to end of Part 3 safety set (~57 months)[1,2]



VCD, virologically confirmed dengue.

1. Tricou V, et al. Efficacy and safety of Takeda's tetravalent dengue vaccine candidate (TAK-003) after 4.5 years of follow-up. Presented at NECTM, Rotterdam, Netherlands, 8–10 June 2022; 2. Takeda. Data on File.

Efficacy against hospitalized VCD: by baseline serostatus and serotype

1st dose to end of Part 3: Safety set (~57 months)[1]

Sensitivity analysis excluding data from Sri Lanka			
	Placebo n 5987	TAK 003 n 11,986	VE (95% CI)
Hospitalized VCD, n (per 100 person-years)			
Seropositive			
DENV-1	22 (0.1)	11 (<0.1)	**75.1** (48.7, 87.9)
DENV-2	18 (<0.1)	2 (<0.1)	**94.4** (76.0, 98.7)
DENV-3	11 (<0.1)	5 (<0.1)	**78.3** (37.4, 92.4)
DENV-4	2 (<0.1)	0 (0.0)	**100** (NE, NE)
Seronegative			
DENV-1	12 (0.2)	5 (<0.1)	**78.9** (40.1, 92.6)
DENV-2	3 (<0.1)	0 (0.0)	**100** (NE, NE)
DENV-3	3 (<0.1)	5 (<0.1)	**15.3** (−254.4, 79.8)
DENV-4	1 (<0.1)	0 (0.0)	**100** (NE, NE)

Rate of hospitalization among VCD cases in placebo group: The Philippines, 17/191 (**8.9%**); Sri Lanka, 70/103 (**68.0%**); Thailand, 25/64 (**39.1%**); Brazil, 2/24 (**8.3%**); Colombia, 14/87 (**16.1%**); Dominican Republic, 4/22 (**18.2%**); Nicaragua, 8/24 (**33.3%**); Panama, 2/45 (**4.4%**).

n refers to number of participants in the safety set. Numbers of hospitalized VCD (per 100 person-years) are based on the number of participants evaluated.

Seronegative at baseline: seronegative to all four DENV serotypes. Seropositive at baseline: reciprocal neutralizing titer ≥10 for one or more DENV serotypes.

CI, confidence interval; DENV, dengue virus; NE, non-estimable; VCD, virologically confirmed dengue; VE, vaccine efficacy.

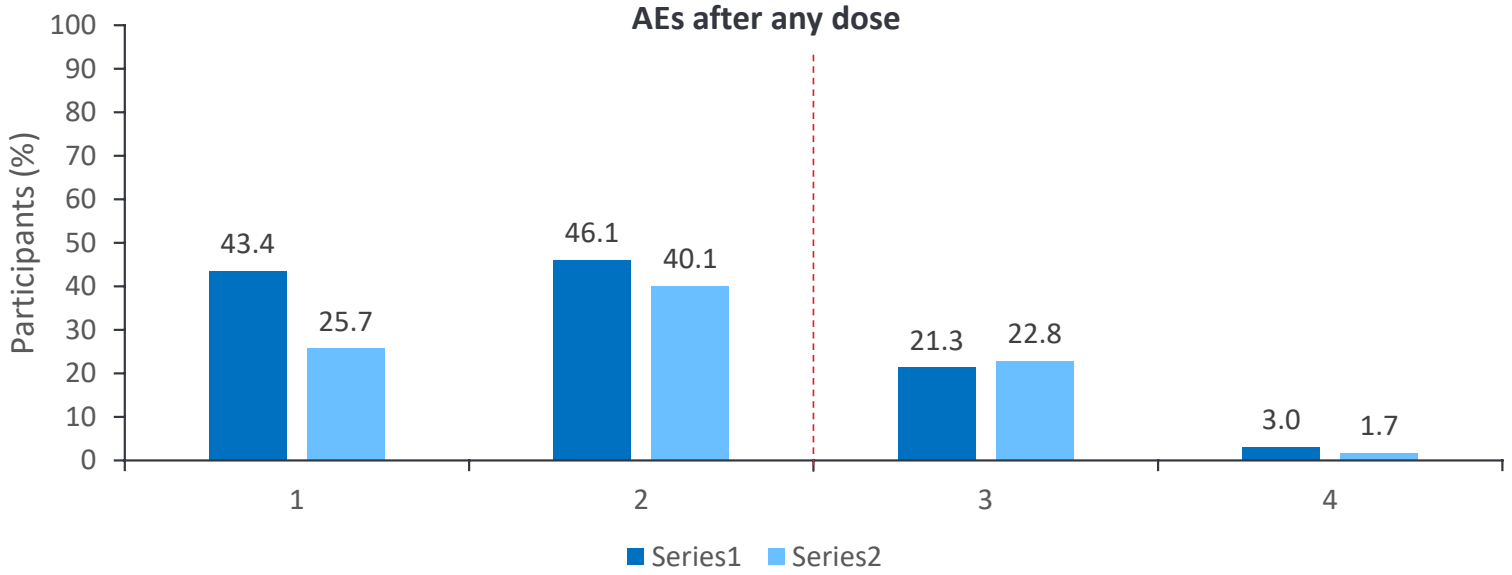
1. Takeda. Data on File.

Safety: Integrated analysis of placebo-controlled trials

Integrated safety analysis

Solicited local (within 7 days), systemic (within 14 days), and unsolicited (within 28 days) AEs in participants aged 4–60 years old[1,2]

- Solicited reactions occurred more frequently in the TAK-003 arm
- Similar reporting of unsolicited AEs in the TAK-003 and placebo arms
- Most frequent TAK-003-related unsolicited AEs: injection-site pruritus (0.7%), bruising (0.6%), and pyrexia (0.2%)



*Injection-site pain, erythema, and swelling; †For adults and children ≥6 years old: headache, myalgia, malaise, asthenia, and fever; for children <6 years old: irritability/fussiness, drowsiness, loss of appetite, and fever.
AE, adverse event.
Solicited AEs: n=3783 (TAK-003) and n=1703 (placebo); Unsolicited AEs: n=3830 (TAK-003) and n=1725 (placebo).
1. Patel S. Presented at ASTMH 2021, National Harbor, MD, US, 17–21 November 2021; 2. Takeda. Data on File: Integrated safety analysis of placebo-controlled trials, Takeda.

Integrated safety analysis: SAEs

Participants with event, n (%)*		Placebo n 7167
Any related SAE	1 (<0.01)	4 (0.06)
SAEs (by preferred term) experienced by >0.2% of participants		
Appendicitis	104 (0.71)	48 (0.67)
Dengue fever†	77 (0.53)	144 (2.01)
Gastroenteritis	52 (0.36)	21 (0.29)
Viral infection	41 (0.28)	40 (0.56)
Asymptomatic COVID-19‡	37 (0.25)	13 (0.18)
Pneumonia	36 (0.25)	24 (0.33)
Urinary tract infection	34 (0.23)	21 (0.29)
COVID-19‡	32 (0.22)	11 (0.15)
Influenza	31 (0.21)	20 (0.28)
DHF†	14 (0.10)	37 (0.52)

One SAE was considered related to TAK-003, compared with five related SAEs in four placebo recipients

Deaths**

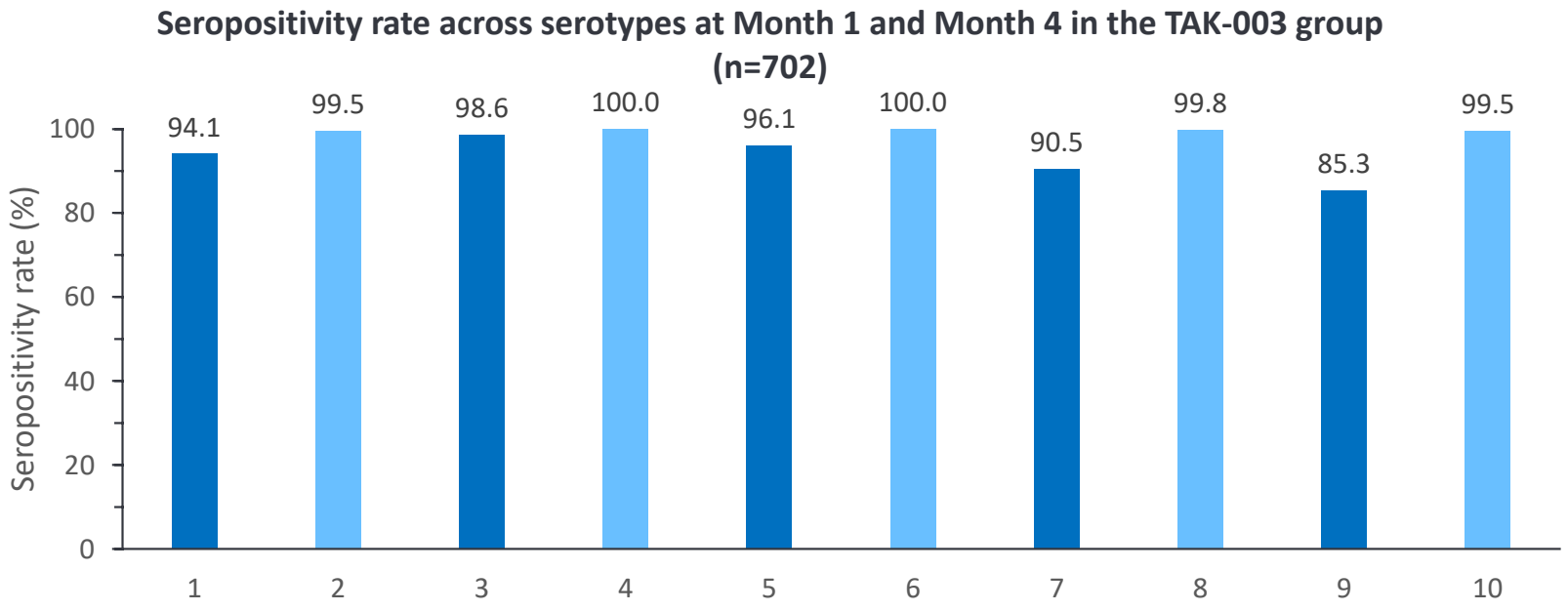
- 16 (0.09%) in the TAK-003 group
- 9 (0.11%) in the placebo group
- None were considered related to the investigational product
- No fatal cases of dengue occurred

*Placebo-controlled trials pool; includes SAEs up to 54 months post 2nd dose in DEN-301; †As reported by investigators: not necessarily virologically confirmed dengue fever or meeting WHO 97 DHF criteria;
‡As per local practice in Sri Lanka and Thailand, symptomatic and asymptomatic COVID-19-positive participants were isolated in designated centers/hospitals, and therefore, cases met SAE criteria;
**All trials pool: n=16,919 (TAK-003), n=8381 (placebo).
DHF, dengue hemorrhagic fever; SAE, serious adverse event; WHO, World Health Organization.
Takeda. Data on File: Integrated safety analysis of placebo-controlled trials including data from DEN-301 up to end of Part 3.

Immunogenicity in baseline seronegative participants

Immunogenicity data: Seropositivity rate

PPSI – participants seronegative at baseline in pivotal efficacy trial (TIDES)



PPSI: number of participants evaluated at each time point may vary. Percentages are based on the number of participants evaluated.
Seropositive: reciprocal neutralizing titer ≥10.
DENV, dengue virus; M, month; PPSI, per protocol set of immunogenicity.
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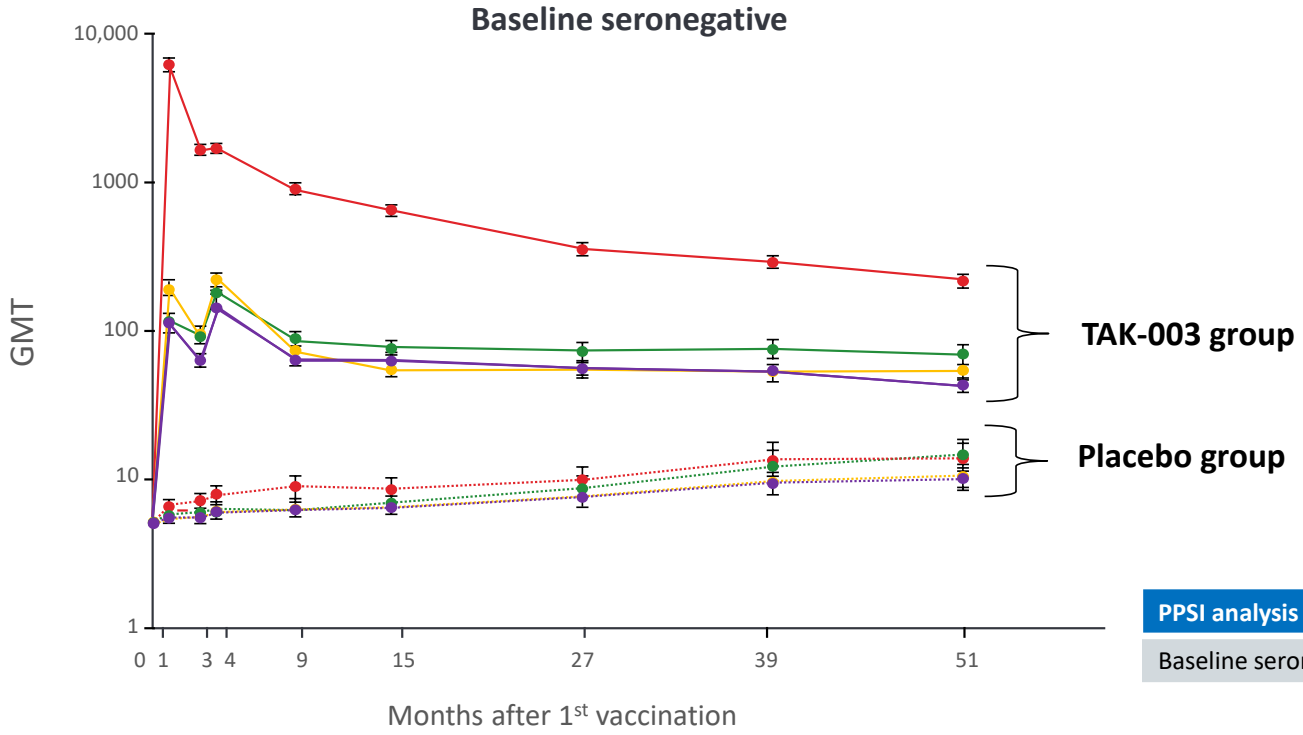
Immunogenicity data: GMT*

PPSI – participants seronegative at baseline in pivotal efficacy trial (TIDES)



PPSI analysis set	TAK 003	Placebo
Baseline seronegatives	n=702	n=345

PPSI: number of participants evaluated at each time point may vary. Percentages are based on the number of participants evaluated.
*Titers expressed as the reciprocal of the highest dilution of test serum that shows a 50% reduction in plaque counts compared with that of virus controls.
DENV, dengue virus; GMT, geometric mean titer; PPSI, per protocol set of immunogenicity.
Takeda. Data on File.

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Summary

- Data from the TIDES pivotal trial showed:
  - **Long-term efficacy of TAK-003 in both baseline seronegative and seropositive participants**
  - **TAK-003 is immunogenic against each of DENV-1, -2,-3, -4 serotypes**

- Data from pivotal trial suggested varying TAK-003 efficacy profiles by serotype
  - **Efficacious against all four serotypes in baseline seropositive participants**
  - **Efficacious against DENV-1 and DENV-2 in baseline seronegative participants**
  - **Among baseline seronegative participants:**
    - **Data suggested lack of efficacy against DENV-3**
    - **The trial did not allow assessment of DENV-4 due to low incidence**
    - **Long-term follow-up did not conclude a higher risk of hospitalized or severe forms of dengue associated with TAK-003 and DENV-3 or -4 serotype**
    - **Totality of data did not indicate harm**

- Safety data from integrated analysis of placebo-controlled trials showed:
  - **TAK-003 had an acceptable safety profile**

DENV, dengue virus. Takeda. Data on File.

Thank you