SUPPLEMENTARY MATERIAL TO CID/ciab864

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Analysis sets

The randomized set consists of all randomized participants, regardless of whether any dose of the investigational product (vaccine or placebo) was received; participants are summarized according to the investigational product to which they were assigned. The safety set consists of all randomized participants who received at least one dose of investigational product (vaccine or placebo); participants are summarized according to the investigational product received. The full-analysis set (FAS) consists of all randomized participants who received at least one dose of investigational product (vaccine or placebo); participants are summarized according to the investigational product to which they were assigned. The FAS for immunogenicity (FASI) consists of all randomized participants in the FAS for whom a valid pre-injection and at least one valid post-injection blood sample were obtained for immunogenicity assessment. The per-protocol set (PPS) consists of all participants in the FAS with no major protocol violations. The PPSI consists of all participants in the FASI with no major protocol violations. Correlate of Protection Set: consists of all PPS participants in the immunogenicity subset or with virologically-confirmed dengue fever cases. The major protocol violations leading to exclusion from the PPS include: 1) not meeting selected entry criteria; 2) receiving incorrect trial vaccine; 3) receiving prohibited therapies; 4) not receiving two doses of trial vaccine or receiving the second dose inadmissibly outside of the visit window; and 5) other major protocol violations identified during blinded data reviews (as stated in study protocol and statistical analysis plan).

Severe dengue case criteria: Dengue Case Adjudication Committee

The Dengue Case Severity Adjudication Committee (DCAC) consists of four members: a voting chairperson, two voting members, and an independent non-voting statistician. The three DCAC voting members are all physicians and clinical dengue experts. DCAC members are not study investigators and do not have any conflict of interest that would bias their review of the trial data. All non-hospitalized cases were considered non-severe by the sponsor.

The assessment of virologically-confirmed hospitalized dengue cases were performed in a blinded manner based on the following criteria: 1) bleeding abnormality, for a case to be considered severe there needs to be a significant intervention required in response to the bleeding episode such as blood transfusion, nasal packing, hormonal therapy, or, bleeding occurred into critical organs such as the brain; 2) plasma leakage, for a case to be considered severe there needs to be evidence of both plasma leakage and functional impairment (plasma leakage includes clinical evidence, radiological evidence, or hematocrit elevated > 20% above normal levels or baseline; functional impairment defined as shock or respiratory distress); 3) liver, for a case to be considered severe there needs to be evidence of both hepatitis and functional impairment (hepatitis defined as an aspartate aminotransferase [AST] or alanine aminotransferase [ALT] > 10 upper limit of normal range [ULN]; functional impairment defined as prothrombin [PT] > 1.5 ULN or hypoalbuminemia); 4) renal, serum creatinine > 2.5 times ULN or requiring dialysis; 5) cardiac, abnormalities intrinsic to the heart (i.e. not resulting from intravascular volume depletion) and with evidence of functional impairment (examples of intrinsic abnormality: myocarditis, pericarditis, and myopericarditis; example of functional impairment: new conduction abnormality resulting in

irregular heart rhythm [i.e. not transient first-degree heart block]); 6) central nervous system, any abnormality with the exception of a simple febrile convulsion or a brief delirium; 7) shock, all shock cases considered severe.

Febrile surveillance methodology to detect symptomatic dengue cases

	ACTIVE SURVEILLANCE (Part 1; Part 2)	**MODIFIED ACTIVE SURVEILLANCE** (Part 3 and booster evaluation phase)	
Contact Frequency	At least weekly	At least weekly	
Threshold for Evaluation	All febrile illness (irrespective of the need for hospitalization)	Febrile illness requiring hospitalization	Febrile illness not requiring hospitalization (unless with alternate laboratory-confirmed etiology)*
Laboratory Evaluations	• Within five days of the onset of fever: RT-PCR; ELISA (NS1, IgM, IgG); platelet count; hematocrit; liver function (ALT & AST) • 7 – 14 days after obtaining acute sample: ELISA (IgM, IgG); platelet count; hematocrit; liver function (ALT & AST) • Other laboratory evaluations as per standard of care		• Within five days of the onset of fever: RT-PCR • Other laboratory evaluations as per standard of care

ALT, alanine aminotransferase; AST, aspartate aminotransferase; NS1, non-structural [dengue] protein 1; RT-PCR and ELISA assays performed at a central laboratory; platelet counts, hematocrit, liver function, and 'other' laboratory evaluations performed at local sites; *no laboratory evaluation (ie, RT-PCR) for a febrile illness that does not require hospitalization and has an alternate laboratory-confirmed etiology during Part 3 and booster evaluation phase.

Exploratory Analyses

Correlate of Protection

In a descriptive approach to evaluate a potential correlate of protection, geometric mean titers (GMTs) were compared between participants who had VCD between one month after second dose and until 18 months after second dose (approximately Month 4 to Month 21 after first dose), referred to as cases, and those who did not have VCD, referred to as controls, overall and by baseline serostatus based on Month 4 MNT titers (one month after second dose). The correlate of protection subset of the PPS used for the correlate of protection analyses included 1404 participants in the placebo group and 2603 participants in the TAK-003 group.

Correlate of Risk of VCD

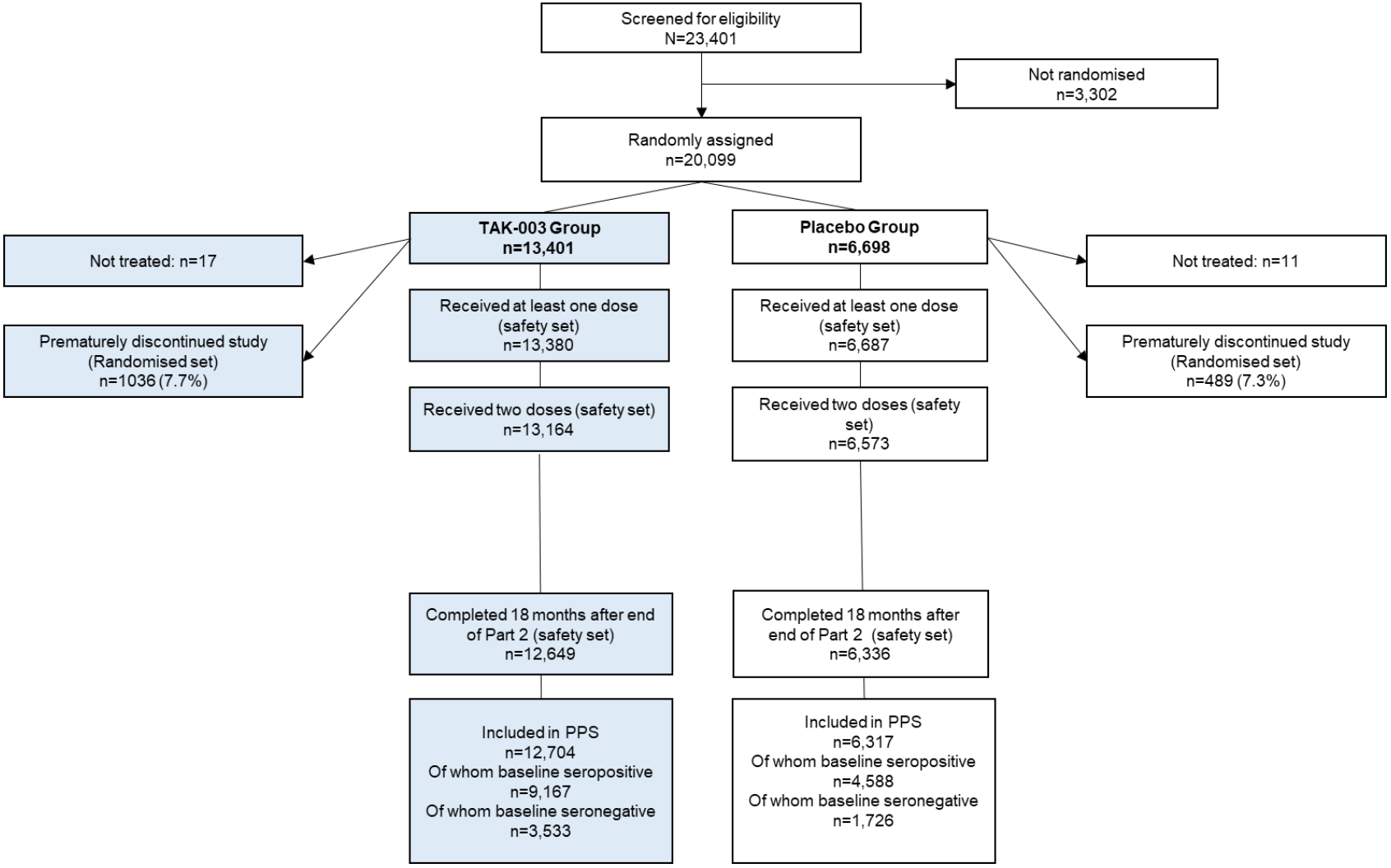
Individual serotype-specific titers at Month 4 were categorized into “low”, “medium” or “high” terciles. Hazard ratios and two-sided 95% CIs were estimated for risk of VCD between one and 18 months after the second dose (approximately Month 4 to Month 21 after first dose) using Cox proportional hazards regressions models, with serotype-specific GMT as a covariate, adjusted for age and stratified by region.

Immunobridging

Baseline seronegative participants were compared with baseline seronegative participants aged 18–60 years enrolled in a separate Phase 3 lot-to-lot consistency study performed in areas of the United States considered non-endemic for dengue (NCT03423173). Adjusted GMTs, geometric mean ratios (GMRs) between the two study populations, and corresponding 95% CIs were calculated using an ANOVA model with comparison group as

factor. Baseline GMTs were imputed as 5.0 (half the lower limit of detection). Non-inferiority for given serotype was to be concluded if upper bound of 95% CI for the geometric mean ratio is below 2. Overall non-inferiority of immune response was to be concluded if null-hypothesis is rejected for all four serotypes, therefore no multiplicity adjustment was planned.

Supplementary Figure 1. Trial Profile. Some data may differ from that previously published due to the inclusion of updated datasets [16-18]. Four participants received both TAK-003 and placebo because of an administrative error and are therefore excluded from the data presentation by vaccination group.



Supplementary Table 1. Vaccine efficacy against virologically-confirmed dengue (VCD) and hospitalized VCD by age from the first dose to three years after the second dose (approximately Month 39 after the first dose; safety set data) in participants who were seronegative at baseline

	Placebo			TAK-003			Vaccine efficacy (95% CI)	
Age (Years)	**n**	**VCD**	**Hospitalized VCD**	**n**	**VCD**	**Hospitalized VCD**	**VCD**	**Hospitalized VCD**
4	141	14 (3.2)	1 (0.2)	313	17 (1.8)	0 (0.0)	44.4 (-12.8, 72.6)	100 (NE, NE)
5	214	15 (2.3)	4 (0.6)	383	24 (2.0)	4 (0.3)	12.9 (-66.0, 54.3)	45.6 (-117.4, 86.4)
6	250	17 (2.2)	3 (0.4)	488	15 (1.0)	1 (<0.1)	54.4 (8.7, 77.2)	82.3 (-70.4, 98.2)
7	187	17 (3.0)	5 (0.9)	434	14 (1.0)	2 (0.1)	66.0 (31.1, 83.3)	83.2 (13.4, 96.7)
8	210	19 (3.0)	7 (1.1)	433	16 (1.2)	4 (0.3)	60.3 (22.8, 79.6)	71.0 (1.0, 91.5)
9	173	11 (2.1)	4 (0.8)	372	10 (0.9)	1 (<0.1)	59.4 (4.3, 82.7)	88.5 (-3.0, 98.7)
10	164	9 (1.7)	3 (0.6)	323	3 (0.3)	3 (0.3)	83.8 (40.1, 95.6)	51.3 (-141.2, 90.2)
11	144	14 (3.2)	4 (0.9)	265	12 (1.5)	0 (0.0)	51.8 (-4.8, 77.9)	100 (NE, NE)
12	110	10 (3.0)	4 (1.2)	212	2 (0.3)	1 (0.1)	90.4 (56.2, 97.9)	88.3 (-4.8, 98.7)
13	93	5 (1.8)	0 (0.0)	195	6 (1.0)	0 (0.0)	45.3 (-79.4, 83.3)	NE (NE, NE)
14	73	3 (1.3)	0 (0.0)	138	4 (0.9)	0 (0.0)	29.5 (-217.0, 84.3)	NE (NE, NE)
15	43	1 (0.8)	0 (0.0)	92	3 (1.1)	0 (0.0)	-29.9 (-1148.9, 86.5)	NE (NE, NE)
16	30	1 (1.1)	0 (0.0)	66	2 (1.0)	0 (0.0)	36.6 (-599.3, 94.3)	NE (NE, NE)

N refers to number of participants in the safety set evaluated. Numbers of VCD (per 100 person years) are based on the number of participants evaluated. Repeat episodes of VCD excluded from efficacy analysis. CI, confidence interval; DENV, dengue virus; VE, vaccine efficacy; VCD, virologically-confirmed dengue; NE, not estimable

Supplementary Table 2. Vaccine efficacy against virologically-confirmed dengue (VCD) and hospitalized VCD by age from the first dose to three years after the second dose (approximately Month 39 after the first dose; safety set data) in participants who were seropositive at baseline

	Placebo			TAK-003			Vaccine efficacy (95% CI)	
Age (Years)	**n**	**VCD**	**Hospitalized VCD**	**n**	**VCD**	**Hospitalized VCD**	**VCD**	**Hospitalized VCD**
4	214	24 (3.9)	3 (0.5)	428	26 (2.0)	6 (0.4)	50.6 (13.9, 71.6)	3.1 (−287.4, 75.8)
5	277	28 (3.4)	3 (0.3)	578	31 (1.7)	1 (<0.1)	48.7 (14.4, 69.2)	83.8 (−55.3, 98.3)
6	392	39 (3.3)	8 (0.7)	794	28 (1.1)	1 (<0.1)	68.1 (48.2, 80.4)	94.5 (56.3, 99.3)
7	405	38 (3.1)	8 (0.6)	811	22 (0.9)	2 (<0.1)	73.0 (54.4, 84.0)	88.1 (44.2, 97.5)
8	458	34 (2.4)	10 (0.7)	877	27 (1.0)	3 (0.1)	58.6 (31.5, 75.1)	84.0 (41.9, 95.6)
9	416	28 (2.2)	11 (0.8)	849	31 (1.2)	3 (0.1)	48.0 (13.3, 68.8)	87.2 (54.2, 96.4)
10	461	37 (2.6)	7 (0.5)	791	18 (0.7)	3 (0.1)	72.9 (52.4, 84.6)	76.3 (8.3, 93.9)
11	436	28 (2.1)	9 (0.7)	947	18 (0.6)	0 (0.0)	71.9 (49.2, 84.5)	100.00 (NE, NE)
12	469	32 (2.2)	8 (0.5)	957	18 (0.6)	4 (0.1)	73.5 (52.8, 85.1)	76.3 (21.2, 92.9)
13	456	27 (1.9)	11 (0.8)	866	16 (0.6)	2 (<0.1)	69.1 (42.6, 83.3)	90.2 (56.0, 97.8)
14	385	21 (1.8)	5 (0.4)	750	15 (0.6)	0 (0.0)	64.1 (30.3, 81.5)	100.0 (NE, NE)
15	276	13 (1.6)	6 (0.7)	619	8 (0.4)	0 (0.0)	74.7 (39.0, 89.5)	100.0 (NE, NE)
16	209	9 (1.4)	2 (0.3)	396	4 (0.3)	1 (<0.1)	74.5 (16.9, 92.2)	68.0 (−252.9, 97.1)

N refers to number of participants in the safety set evaluated. Numbers of VCD (incidence density as the number of cases per 100 person years) are based on the number of participants evaluated. Repeat episodes of VCD excluded from efficacy analysis. CI, confidence interval; DENV, dengue virus; VE, vaccine efficacy; VCD, virologically-confirmed dengue; NE, not estimable

Supplementary Table 3. Vaccine efficacy (95% CI) of TAK-003 in preventing virologically-confirmed dengue (VCD) during Years 1[a], 2, and 3 after the second dose (per-protocol set data). Data under the placebo and TAK-003 groups are presented as number of VCD/number of evaluable participants (number of VCD cases per 100 person years at risk)

	Placebo	TAK-003	Efficacy % (95% CI)
Seropositive			
DENV-1			
Year 1	17/4587 (0.4)	7/9165 (<0.1)	79.8% (51.3, 91.6)
Year 2	31/4552 (0.7)	26/9078 (0.3)	59.1% (31.1, 75.7)
Year 3	69/4502 (1.7)	77/8968 (0.9)	45.4% (24.5, 60.6)
DENV-2			
Year 1	42/4587 (1.0)	3/9165 (< 0.1)	96.5% (88.8, 98.9)
Year 2	22/4552 (0.5)	11/9078 (0.1)	75.5% (49.5, 88.1)
Year 3	34/4502 (0.8)	20/8968 (0.2)	72.1% (51.6, 84.0)
DENV-3			
Year 1	47/4587 (1.1)	28/9165 (0.3)	71.4% (54.3, 82.1)
Year 2	21/4552 (0.5)	25/9078 (0.3)	44.9% (1.6, 69.2)
Year 3	20/4502 (0.5)	37/8968 (0.4)	15.2% (−46.1, 50.8)
DENV-4			
Year 1	4/4587 (<0.1)	3/9165 (< 0.1)	63.8% (-61.8, 91.9)
Year 2	3/4552 (<0.1)	2/9078 (<0.1)	69.0% (−85.7, 94.8)
Year 3	6/4502 (0.1)	5/8968 (<0.1)	61.9% (−24.9, 88.4)
Seronegative			
DENV-1			
Year 1	13/1726 (0.8)	9/3531 (0.3)	67.2% (23.2, 86.0)
Year 2	18/1715 (1.1)	15/3498 (0.4)	60.7% (22.1, 80.2)
Year 3	28/1698 (1.8)	49/3465 (1.5)	17.2% (−31.8, 47.9)
DENV-2			
Year 1	22/1726 (1.4)	0/3531 (0)	100% (–, –)
Year 2	5/1715 (0.3)	3/3498 (<0.1)	70.5% (−23.4, 93.0)
Year 3	16/1698 (1.0)	5/3465 (0.1)	84.9% (58.7, 94.5)
DENV-3			
Year 1	4/1726 (0.3)	11/3531 (0.3)	−38.7% (-335.7, 55.8)
Year 2	5/1715 (0.3)	12/3498 (0.3)	−18.5% (−236.2, 58.3)
Year 3	6/1698 (0.4)	11/3465 (0.3)	9.5% (−144.7, 66.5)
DENV-4			
Year 1	0/1726 (0.0)	0/3531 (0)	–
Year 2	1/1715 (<0.1)	3/3498 (<0.1)	−47.6% (−1319.1, 84.6)
Year 3	1/1698 (<0.1)	4/3465 (0.1)	−99.0% (−1680.3, 77.8)

Only the first instance of VCD was included in efficacy evaluation. For serotype-specific efficacy calculations, only the first instance of VCD due to the individual serotype in question was included, regardless of previous instances of VCD due to other serotypes. Participants were classified as seronegative when testing seronegative for all dengue serotypes at baseline. Participants were classified as seropositive when demonstrating a reciprocal neutralizing antibody titer ≥ 10 against at least one dengue serotype at baseline.

[a]Data from Lopez-Medina et al, Efficacy of a dengue vaccine candidate (TAK-003) in healthy children and adolescents two years after vaccination. J Infect Dis 2020 Dec 15;jiaa761.doi: 10.1093/infdis/jiaa761

Note that some data in the table may differ from previously published data following updates to the data sets during the ongoing trial

Supplementary Table 4. Clinical signs and symptoms of virologically-confirmed dengue (VCD) cases occurring from the first dose to three years after the second dose (approximately Month 39 after the first dose; safety set data). Includes data of second episodes of VCD.

	Placebo (n = 6687)	**TAK-003** (n = 13380)
Number of VCD Cases	503	392
Duration of Febrile Illness (Days; Median / Mean; 95% CI)*	6.0 / 6.6 (6.3, 6.9)	6.0 / 6.3 (6.0, 6.6)
Duration of Fever (Days; Median / Mean; 95% CI)	5.0 / 4.6 (4.4, 4.7)	4.0 / 4.1 (3.9, 4.2)
Number of Hospitalized VCD Cases	126	42
Duration of Hospitalization (Days; Median / Mean; 95% CI)	5.0 / 5.6 (4.7, 6.5)	5.0 / 5.0 (4.4, 5.6)
Evidence of Bleeding (%, n / N)	8.0% (40/503)	4.8% (19/392)
Plasma Leakage (%, n / N) ¶	4.2% (21/503)	2.3% (9/392)
Hematocrit Increase ≥ 20% (%, n / N)†	12.1% (30/247)	8.0% (10/125)
Platelet Count ≤ 100 x 10^9 / L (%, n / N)‡	22.1% (91/411)	10.2% (27/266)
Platelet Count ≤ 50 x 10^9 / L (%, n / N)‡	9.7% (40/411)	3.8% (10/266)
ALT or AST ≥ 1000 U / L (%, n / N)‡	0.3% (1/341)	0.0% (0/185)
ALT or AST > 10x ULN (%, n / N)	1.8% (6/341)	0.0% (0/185)
Signs of Circulatory Failure (Any) (%, n / N)	0.6% (3/503)	0.5% (2/392)
Reduced Pulse Pressure (%, n / N)	0.4% (2/503)	0.3% (1/392)
Hypotensive Shock (%, n / N)	0.2% (1/503)	0.3% (1/392)

VCD, virologically-confirmed dengue; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal; *duration of febrile illness defined as end date of latest symptom to start date of earliest symptom + 1 day (symptoms considered include fever and any general symptoms); ¶does not include hematocrit increase ≥ 20% reported in a separate row and is based on investigator reporting of clinical evidence of plasma leakage which could include clinical, radiological or laboratory findings; †hematocrit increase defined as maximum hematocrit between Day 3 and Day 7 inclusive, from onset of fever ≥ 20% increase over minimum hematocrit before Day 3 or after Day 7 from onset of fever; ‡for platelet, ALT, and AST data, assessments within 14 days of onset of febrile illness have been considered ('n' in column header refers to number of participants in the Safety Set; 'N' in rows refers to number of VCD cases with available data for specific parameter)

Supplementary Table 5. Clinical signs and symptoms of virologically-confirmed dengue (VCD) cases occurring from the first dose to three years after the second dose (approximately Month 39 after the first dose; safety set data) by serotype in baseline seropositive participants.

	Placebo (n = 4854)				**TAK-003** (n = 9663)			
	DENV-1	**DENV-2**	**DENV-3**	**DENV-4**	**DENV-1**	**DENV-2**	**DENV-3**	**DENV-4**
Number of VCD Cases	130	124	96	15	114	42	94	12
Duration of Febrile Illness (Days; Median / Mean; 95% CI)*	6.0 / 6.6 (5.9, 7.3)	6.0 / 6.2 (5.7, 6.6)	6.0 / 7.1 (6.3, 7.8)	6.0 / 5.8 (4.6, 7.0)	6.0 / 6.4 (5.8, 7.0)	5.0 / 6.0 (5.2, 6.7)	5.0 / 6.2 (5.4, 6.9)	5.5 / 5.2 (3.9, 6.4)
Duration of Fever (Days; Median / Mean; 95% CI)	4.5 / 4.4 (4.1, 4.7)	5.0 / 4.7 (4.4, 5.0)	4.0 / 4.5 (4.1, 4.9)	4.0 / 3.9 (3.3, 4.5)	4.0 / 4.2 (3.9, 4.5)	4.0 / 4.4 (3.9, 4.9)	4.0 / 3.8 (3.5, 4.1)	3.0 / 3.6 (2.6, 4.6)
Number of Hospitalized VCD Cases	21	53	14	3	13	5	8	0
Duration of Hospitalization (Days; Median / Mean; 95% CI)	4.0 / 7.5 (2.1, 12.9)	5.0 / 5.1 (4.6, 5.6)	6.0 / 6.4 (5.0, 7.8)	5.0 / 4.3 (1.5, 7.2)	4.0 / 4.2 (3.2, 5.1)	3.0 / 2.6 (1.9, 3.3)	5.0 / 5.6 (4.6, 6.6)	–
Evidence of Bleeding (%, n / N)	11.5% (15/130)	7.3% (9/124)	7.3% (7/96)	6.7% (1/15)	6.1% (7/114)	0.0% (0/42)	5.3% (5/94)	0.0% (0/12)
Plasma Leakage (%, n / N) ¶	4.6% (6/130)	8.9% (11/124)	1.0% (1/96)	0.0% (0/15)	0.0% (0/114)	2.4% (1/42)	1.1% (1/94)	0.0% (0/12)
Hematocrit Increase ≥ 20% (%, n / N)†	12.5% (6/48)	15.7% (13/83)	19.4% (7/36)	12.5% (1/8)	14.8% (4/27)	0.0% (0/13)	7.7% (3/39)	0.0% (0/5)
Platelet Count ≤ 100 x 10^9 / L (%, n / N)‡	18.9% (17/90)	39.8% (45/113)	14.3% (13/91)	10.0% (1/10)	12.1% (7/58)	5.9% (2/34)	9.8% (8/82)	0.0% (0/9)
Platelet Count ≤ 50 x 10^9 / L (%, n / N)‡	7.8% (7/90)	19.5% (22/113)	5.5% (5/91)	10.0% (1/10)	3.4% (2/58)	2.9% (1/34)	4.9% (4/82)	0.0% (0/9)
ALT or AST ≥ 1000 U / L (%, n / N)‡	1.4% (1/72)	0.0% (0/98)	0.0% (0/70)	0.0% (0/8)	0.0% (0/41)	0.0% (0/26)	0.0% (0/51)	0.0% (0/6)

ALT or AST > 10x ULN (%, n / N)	4.2% (3/72)	2.0% (2/98)	0.0% (0/70)	0.0% (0/8)	0.0% (0/41)	0.0% (0/26)	0.0% (0/51)	0.0% (0/6)
Signs of Circulatory Failure (Any) (%, n / N)	0.8% (1/130)	0.8% (1/124)	1.0% (1/96)	0.0% (0/15)	0.0% (0/114)	0.0% (0/42)	1.1% (1/94)	0.0% (0/12)
Reduced Pulse Pressure (%, n / N)	0.0% (0/130)	0.8% (1/124)	1.0% (1/96)	0.0% (0/15)	0.0% (0/114)	0.0% (0/42)	1.1% (1/94)	0.0% (0/12)
Hypotensive Shock (%, n / N)	0.0% (0/130)	0.8% (1/124)	0.0% (0/96)	0.0% (0/15)	0.0% (0/114)	0.0% (0/42)	0.0% (0/94)	0.0% (0/12)

VCD, virologically-confirmed dengue; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal *duration of febrile illness defined as end date of latest symptom to start date of earliest symptom + 1 day (symptoms considered include fever and any general symptoms); ¶does not include hematocrit increase ≥ 20% reported in a separate row and is based on investigator reporting of clinical evidence of plasma leakage which could include clinical, radiological or laboratory findings; †hematocrit increase defined as maximum hematocrit between Day 3 and Day 7 inclusive, from onset of fever ≥ 20% increase over minimum hematocrit before Day 3 or after Day 7 from onset of fever; ‡for platelet, ALT, and AST data, assessments within 14 days of onset of febrile illness have been considered (‘n’ in column header refers to number of participants in the Safety Set; ‘N’ in rows refers to number of VCD cases with available data for specific parameter)

Supplementary Table 6. Clinical signs and symptoms of virologically-confirmed dengue (VCD) cases occurring from the first dose to three years after the second dose (approximately Month 39 after the first dose; safety set data) for DENV-1, DENV-2, and DENV-4 in baseline seronegative participants.

	Placebo (n = 1832)			**TAK-003** (n = 3714)		
	DENV-1	**DENV-2**	**DENV-4**	**DENV-1**	**DENV-2**	**DENV-4**
Number of VCD Cases	66	55	2	77	9	8
Duration of Febrile Illness (Days; Median / Mean; 95% CI)*	6.0 / 7.5 (6.2, 8.7)	6.0 / 6.1 (5.5, 6.7)	6.0 / 6.0 (−6.7, 18.7)	6.0 / 6.4 (5.7, 7.0)	5.0 / 6.4 (4.1, 8.8)	5.0 / 4.9 (3.4, 6.3)
Duration of Fever (Days; Median / Mean; 95% CI)	5.0 / 4.7 (4.2, 5.2)	5.0 / 4.8 (4.3, 5.3)	3.0 / 3.0 (NE, NE)	4.0 / 4.3 (3.9, 4.7)	3.0 / 3.2 (2.5, 4.0)	4.0 / 4.0 (3.1, 4.9)
Number of Hospitalized VCD Cases	11	22	0	5	0	0
Duration of Hospitalization (Days; Median / Mean; 95% CI)	3.0 / 3.9 (2.6, 5.2)	5.5 / 5.5 (4.8, 6.1)	–	5.0 / 4.8 (2.8, 6.8)	–	–
Evidence of Bleeding (%, n / N)	3.0% (2/66)	3.6% (2/55)	0.0% (0/2)	5.2% (4/77)	0.0% (0/9)	0.0% (0/8)
Plasma Leakage (%, n / N) ¶	0.0% (0/66)	3.6% (2/55)	0.0% (0/2)	0.0% (0/77)	0.0% (0/9)	0.0% (0/8)
Hematocrit Increase ≥ 20% (%, n / N)†	3.1% (1/32)	2.9% (1/34)	0.0% (0/0)	0.0% (0/18)	0.0% (0/0)	0.0% (0/1)
Platelet Count ≤ 100 x 10^9 / L (%, n / N)‡	11.8% (6/51)	17.8% (8/45)	0.0% (0/0)	4.9% (2/41)	0.0% (0/4)	0.0% (0/5)
Platelet Count ≤ 50 x 10^9 / L (%, n / N)‡	3.9% (2/51)	6.7% (3/45)	0.0% (0/0)	2.4% (1/41)	0.0% (0/4)	0.0% (0/5)
ALT or AST ≥ 1000 U / L (%, n / N)‡	0.0% (0/46)	0.0% (0/39)	0.0% (0/0)	0.0% (0/31)	0.0% (0/1)	0.0% (0/1)
ALT or AST > 10x ULN (%, n / N)	0.0% (0/46)	2.6% (1/39)	0.0% (0/0)	0.0% (0/31)	0.0% (0/1)	0.0% (0/1)
Signs of Circulatory Failure (Any) (%, n / N)	0.0% (0/66)	0.0% (0/55)	0.0% (0/2)	0.0% (0/77)	0.0% (0/9)	0.0% (0/8)
Reduced Pulse Pressure (%, n / N)	0.0% (0/66)	0.0% (0/55)	0.0% (0/2)	0.0% (0/77)	0.0% (0/9)	0.0% (0/8)
Hypotensive Shock (%, n / N)	0.0% (0/66)	0.0% (0/55)	0.0% (0/2)	0.0% (0/77)	0.0% (0/9)	0.0% (0/8)

VCD, virologically-confirmed dengue; ALT, alanine aminotransferase; AST, aspartate aminotransferase; NE, non-estimable; ULN, upper limit of normal *duration of febrile illness defined as end date of latest symptom to start date of earliest symptom + 1 day (symptoms considered include fever and any general symptoms); ¶does not include hematocrit increase ≥ 20% reported in a separate row and is based on investigator reporting of clinical evidence of plasma leakage which could include clinical examinations, radiological or laboratory findings; †hematocrit increase defined as maximum hematocrit between Day 3 and Day 7 inclusive, from onset of fever ≥ 20% increase over minimum hematocrit before Day 3 or after Day 7 from onset of fever; ‡for platelet, ALT, and

AST data, assessments within 14 days of onset of febrile illness have been considered (‘n’ in column header refers to number of participants in the Safety Set; ‘N’ in rows refers to number of VCD cases with available data for specific parameter)

Supplementary Table 7. Virologically-confirmed dengue (VCD), hospitalized VCD, severe forms of dengue, and frequency of platelet count and ultrasound evaluations in the placebo group in and outside of Sri Lanka, from the first dose to three years after the second dose (approximately Month 39 after the first dose; safety set data)

Variable	Sri Lanka	Outside Sri Lanka
Number of Subjects	700	5987
Number of VCD cases	100	403
Leading to hospitalization, n (%)	68 (68.0)	58 (14.4)*
At least 1 platelet count evaluation per case, n (%)	100 (100)	311 (77.2)
Mean number of platelet count evaluations per case	9.1	1.1 to 3.7#
Ultrasound evaluation		
At least 1 ultrasound evaluation per case, n (%)	63 (63.0)	8 (2.0)
Mean number of ultrasound evaluations per case	3.4	0.1 to 0.1
DCAC-defined severe VCD, n (%)	0 (0)	5 (1.2)
DHF (WHO criteria 1997), n (%)	5 (5.0)	8 (2.0)

DCAC, dengue case adjudication committee; DHF, dengue hemorrhagic fever; VCD, virologically-confirmed dengue

* Range 2.5% (1/40) in Panama to 37.7% (20/53) in Thailand

The range of means across the 7 countries other than Sri Lanka with available data is presented.

Supplementary Table 8. Clinical signs and symptoms of virologically-confirmed dengue (VCD) cases occurring from the first dose to three years after the second dose (approximately Month 39 after the first dose; safety set data) for DENV-3 in baseline seronegative participants including and excluding Sri Lanka data in the trial.

	Placebo		TAK-003	
	Including Sri Lanka (N=1832)	**Excluding Sri Lanka (N=1564)**	**Including Sri Lanka (N=3714)**	**Excluding Sri Lanka (N=3181)**
Number of VCD Cases	15	15	36	30
Duration of Febrile Illness (Days; Median / Mean; 95% CI)*	6.0 / 6.9 (4.9, 8.8)	6.0 / 6.9 (4.9, 8.8)	6.5 / 7.3 (5.9, 8.6)	6.0 / 7.3 (5.7, 8.9)
Duration of Fever (Days; Median / Mean; 95% CI)	4.0 / 4.6 (3.5, 5.7)	4.0 / 4.6 (3.5, 5.7)	4.0 / 4.1 (3.6, 4.6)	3.5 / 3.7 (3.3, 4.2)
Number of Hospitalized VCD Cases	2	2	11	5
Duration of Hospitalization (Days; Median / Mean; 95% CI)	4.5 / 4.5 (−1.9, 10.9)	4.5 / 4.5 (−1.9, 10.9)	7.0 / 6.6 (5.7, 7.6)	7.0 / 6.6 (4.3, 8.9)
Number of DCAC-defined severe VCD or DHF (WHO Criteria 1997) cases†	1	1	5	3
Evidence of Bleeding (%, n / N)	26.7% (4/15)	26.7% (4/15)	8.3% (3/36)	6.7% (2/30)
Plasma Leakage (%, n / N) ¶	6.7% (1/15)	6.7% (1/15)	19.4% (7/36)	10.0% (3/30)
Hematocrit Increase ≥ 20% (%, n / N)†	16.7% (1/6)	16.7% (1/6)	13.6% (3/22)	12.5% (2/16)
Platelet Count ≤ 100 x 10^9 / L (%, n / N)‡	9.1% (1/11)	9.1% (1/11)	24.2% (8/33)	11.1% (3/27)
Platelet Count ≤ 50 x 10^9 / L (%, n / N)‡	0.0% (0/11)	0.0% (0/11)	6.1% (2/33)	3.7% (1/27)
ALT or AST ≥ 1000 U / L (%, n / N)‡	0.0% (0/8)	0.0% (0/8)	0.0% (0/28)	0.0% (0/22)
ALT or AST > 10x ULN (%, n / N)	0.0% (0/8)	0.0% (0/8)	0.0% (0/28)	0.0% (0/22)
Signs of Circulatory Failure (Any) (%, n / N)	0.0% (0/15)	0.0% (0/15)	2.8% (1/36)	3.3% (1/30)
Reduced Pulse Pressure (%, n / N)	0.0% (0/15)	0.0% (0/15)	0.0% (0/36)	0.0% (0/30)
Hypotensive Shock (%, n / N)	0.0% (0/15)	0.0% (0/15)	2.8% (1/36)	3.3% (1/30)

VCD, virologically-confirmed dengue; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal *duration of febrile illness defined as end date of latest symptom to start date of earliest symptom + 1 day (symptoms considered include fever and any general symptoms); †one case in the TAK-003 group met criteria for both DCAC-defined severe dengue and DHF; ¶does not include hematocrit increase ≥ 20% reported in a separate row and is based on investigator reporting of clinical evidence of plasma leakage which could include clinical examinations, radiological or laboratory findings; †hematocrit increase defined as maximum hematocrit between Day 3 and Day 7 inclusive, from onset of fever ≥ 20% increase over minimum hematocrit

before Day 3 or after Day 7 from onset of fever; ‡for platelet, ALT, and AST data, assessments within 14 days of onset of febrile illness have been considered (‘n’ in column header refers to number of participants in the Safety Set; ‘N’ in rows refers to number of VCD cases with available data for specific parameter)

Supplementary Table 9. Mean (95% confidence interval) serotype-specific dengue RNA titers (expressed as log10, copies / mL) for virologically-confirmed dengue (VCD) cases occurring from the first dose to three years after the second dose (approximately Month 39 after the first dose; safety set data). Dengue RNA was detected and quantified with a validated serotype specific RT-PCR assay on acute febrile illness sample. The upper limit of quantification (ULoQ) was determined to be 85,714,286 genome copy equivalents (GCE) / mL (log10 [ULoQ] = 7.9) for all four dengue serotypes. Dengue RNA samples with an RT-PCR value above the ULoQ were quantified by extrapolation using a linear standard curve model.

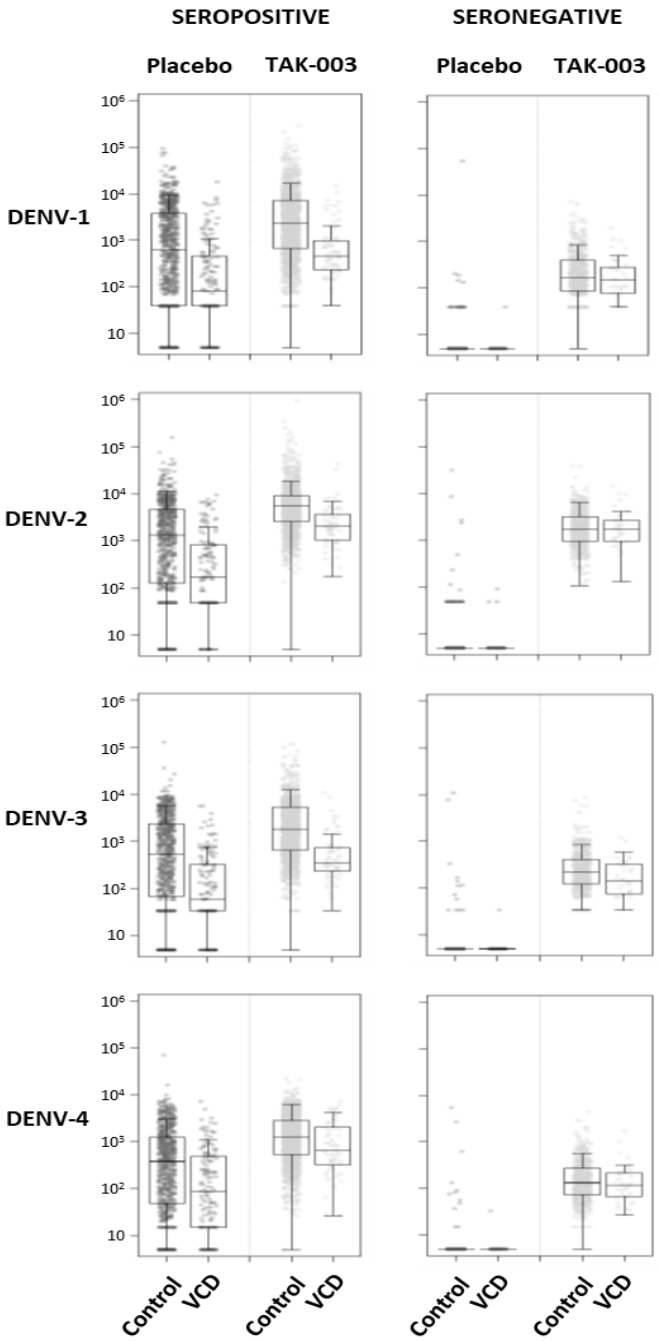
	Placebo			TAK-003		
Serotype	**No. VCD cases (hospitalized)**	**VCD**	**Hospitalized VCD**	**No. VCD cases (hospitalized)**	**VCD**	**Hospitalized VCD**
Baseline seronegative						
DENV-1	66 (11)	6.78 (6.38, 7.18)	6.71 (5.56, 7.87)	77 (5)	6.57 (6.27, 6.87)	5.78 (3.81, 7.76)
DENV-2	55 (22)	7.10 (6.72, 7.48)	7.60 (7.02, 8.17)	9 (0)	6.74 (5.75, 7.72)	--
DENV-3	15 (2)	6.81 (5.87, 7.76)	7.99 (−10.09, 26.06)	36 (11)	7.02 (6.44, 7.60)	7.33 (5.86, 8.81)
DENV-4	2 (0)	5.98 (−10.92, 22.88)	--	8 (0)	5.40 (4.55, 6.25)	--
Baseline seropositive						
DENV-1	130 (21)	7.08 (6.82, 7.33)	7.55 (6.97, 8.14)	114 (13)	6.34 (6.09, 6.58)	6.53 (5.51, 7.55)
DENV-2	124 (53)	7.82 (7.58, 8.06)	7.82 (7.43, 8.21)	42 (5)	6.26 (5.86, 6.67)	6.57 (4.80, 8.35)
DENV-3	96 (14)	7.44 (7.10, 7.77)	6.88 (5.61, 8.14)	94 (8)	7.25 (6.96, 7.54)	7.18 (5.79, 8.56)
DENV-4	15 (3)	6.02 (5.23, 6.81)	4.49 (3.02, 5.96)	12 (0)	5.36 (4.52, 6.21)	--

VCD, virologically-confirmed dengue

Supplementary Table 10. Number of participants experiencing serious adverse events (by system organ class and preferred term) occurring after any vaccination during first half of Part 3 (approximately Month 22 to Month 39 after the first dose/Month 19 to Month 36 after the second dose; safety set data). Four participants received both TAK-003 and placebo and are therefore excluded from the data by vaccination columns but included in the total participants column. *Data not presented by TAK-003 and placebo groups to prevent unblinding.

System Organ Class / Preferred Term	**Placebo** Number (%)	**TAK-003** Number (%)	**Total** Number (%)
Number of Participants in the Safety Set	6687	13,380	20,071
Any Adverse Event	234 (3.5)	386 (2.9)	620 (3.1)
Infections & Infestations	169 (2.5)	248 (1.9)	417 (2.1)
Injury, Poisoning, & Procedural Complications	24 (0.4)	57 (0.4)	81 (0.4)
Gastrointestinal Disorders	13 (0.2)	19 (0.1)	32 (0.2)
Pregnancy, Puerperium, & Perinatal Conditions	10 (0.1)	18 (0.1)	28 (0.1)
Psychiatric Disorders	3 (<0.1)	19 (0.1)	22 (0.1)
Nervous System Disorders	9 (0.1)	12 (<0.1)	21 (0.1)
Metabolism & Nutritional Disorders	6 (<0.1)	5 (<0.1)	11 (<0.1)
Respiratory, Thoracic, & Mediastinal Disorders	4 (<0.1)	5 (<0.1)	9 (<0.1)
Blood & Lymphatic System Disorders	3 (<0.1)	6 (<0.1)	9 (<0.1)
Renal & Urinary Disorders	2 (<0.1)	6 (<0.1)	8 (<0.1)
Neoplasms	4 (<0.1)	2 (<0.1)	6 (<0.1)
Musculoskeletal & Connective Tissue Disorders	3 (<0.1)	2 (<0.1)	5 (<0.1)
General Disorders & Administration Site Conditions	3 (<0.1)	2 (<0.1)	5 (<0.1)
Immune System Disorders	2 (<0.1)	2 (<0.1)	4 (<0.1)
Vascular Disorders	3 (<0.1)	1 (<0.1)	4 (<0.1)
Skin & Subcutaneous Tissue Disorders	1 (<0.1)	3 (<0.1)	4 (<0.1)
Congenital, Familial, & Genetic Disorders	1 (<0.1)	2 (<0.1)	3 (<0.1)
Reproductive System & Breast Disorders	1 (<0.1)	2 (<0.1)	3 (<0.1)
Social Circumstances*	-	-	2 (<0.1)
Eye Disorders*	-	-	2 (<0.1)
Hepatobiliary Disorders*	-	-	1 (<0.1)
Investigations*	-	-	1 (<0.1)
Cardiac Disorders*	-	-	1 (<0.1)

Supplementary Figure 2. Distribution of serotype-specific antibody titers at Month 4 (i.e. one month after second dose) in dengue cases occurring between 1 month after the second dose and until 18 months after the second dose (approximately Month 4 to Month 21 after the first dose; per protocol set – correlate of protection subset data). Controls include all participants in the subset who did not have virologically-confirmed dengue (VCD) between Month 4 to Month 21. Cases include all participants in the study who had VCD after Month 4 to Month 21.



Box plots show the 25th percentile (lower edge of the box), 50th percentile (horizontal line in the box), and 75th percentile (upper edge of the box), with participants stratified according to dengue case/control status and treatment assignment; the whiskers indicate the most extreme data points, which are no more than 1.5 times the interquartile range from the box.

Supplementary Table 11. Correlate of risk of VCD analysis between 1 month after second dose and until 18 months after the second dose (approximately Month 21 after the first dose; per protocol set – correlate of protection subset data) and by baseline serostatus based on neutralizing antibody titers one month after the second dose (Month 4)

		Medium vs Low Titer [(a)]		High vs Low Titer [(a)]	
Serotype	**Statistic [(b)]**	**Placebo**	**TAK-003**	**Placebo**	**TAK-003**
Overall					
DENV-1	**Hazard ratio**	0.448	0.507	0	0
	95% CI	(0.196, 1.024)	(0.259, 0.993)	(0, 0)	(0, 0)
DENV-2	**Hazard ratio**	0.244	NE	0.022	NE
	95% CI	(0.106, 0.560)	(NE, NE)	(0.003, 0.163)	(NE, NE)
DENV-3	**Hazard ratio**	0.932	0.543	0	0.024
	95% CI	(0.484, 1.793)	(0.321, 0.918)	(0, 0)	(0.003, 0.181)
DENV-4	**Hazard ratio**	0	0.537	0	0
	95% CI	(0, 0)	(0.071, 4.056)	(0, 0)	(0, 0)
Baseline seropositive					
DENV-1	**Hazard ratio**	0.154	0.445	0	0
	95% CI	(0.036, 0.653)	(0.171, 1.156)	(0, 0)	(0, 0)
DENV-2	**Hazard ratio**	0.117	0.398	0.028	0.169
	95% CI	(0.040, 0.340)	(0.043, 3.720)	(0.004, 0.210)	(0.016, 1.819)
DENV-3	**Hazard ratio**	0.183	0.217	0	0
	95% CI	(0.056, 0.596)	(0.102, 0.462)	(0, 0)	(0, 0)
DENV-4	**Hazard ratio**	0	0.393	0	0
	95% CI	(0, 0)	(0.031, 4.931)	(0, 0)	(0, 0)
Baseline seronegative					
DENV-1	**Hazard ratio**	0	NE	0	NE
	95% CI	(0, 0)	(NE, NE)	(0, 0)	(NE, NE)
DENV-2	**Hazard ratio**	0.258	0.398	0	0.169
	95% CI	(0.033, 1.987)	(0.043, 3.720)	(0, 0)	(0.016, 1.819)
DENV-3	**Hazard ratio**	0	0.483	0	0.288
	95% CI	(0, 0)	(0.098, 2.381)	(0, 0)	(0.054, 1.542)
DENV-4	**Hazard ratio**	NE	NE	NE	1.033
	95% CI	(NE, NE)	(NE, NE)	(NE, NE)	(0.136, 7.839)

CI, confidence interval; NE, non-estimable.

(a) Low, medium, and high titer subgroups defined by weighted tertiles of Month 4 titers pooling over the 4 serotypes and over the TAK-003 and placebo groups. The weights are defined to account for the case-cohort biomarkers sampling design.

(b) Hazard ratio ($\lambda V / \lambda C$) and 2-sided 95% CI estimated from the Cox proportional hazards regression models for each treatment group including the serotype-specific geometric mean titer as covariate adjusting for age and stratified by region.

If there were no cases in the medium or high tertiles compared with the low tertile, the hazard ratio was 0. If there no cases in the low tertile, the hazard ratio was non-estimable. A greater than 1 hazard ratio is in favor of low tertile group in the comparison, a less than 1 hazard ratio is in favor of medium or high tertile group, within either placebo group or TAK-003 group.

Supplementary Table 12. Adjusted geometric mean titers (GMTs) of dengue neutralizing antibodies for each serotype for baseline seronegative participants aged 4–16 years in the DEN-301 study in Per Protocol Set of Immunogenicity (NCT02747927) and aged 18–60 years in the DEN-304 study (NCT03423173) – per-protocol set data. Month 4 refers to one month after the second dose; Month 9 refers to six months after the second dose

Serotype	Visit	DEN-301 (N = 702)		DEN-304 (N = 379)		
		n	Adjusted GMT (95% CI) [(a)]	n	Adjusted GMT (95% CI) [(a)]	GMR (95% CI) [(a)]
DENV-1	**Month 4**	641	184.2 (165.9, 204.6)	367	268.1 (233.5, 307.9)	**0.69 (0.58, 0.82)**
	Month 9	607	87.8 (77.8, 99.2)	353	141.7 (120.9, 166.1)	**0.62 (0.51, 0.76)**
DENV-2	**Month 4**	641	1730.2 (1603.1, 1867.3)	367	2956.9 (2673.4, 3270.4)	**0.59 (0.52, 0.66)**
	Month 9	607	929.4 (851.7, 1014.1)	355	1403.3 (1251.9, 1572.9)	**0.66 (0.57, 0.76)**
DENV-3	**Month 4**	641	228 (209.2, 248.5)	367	128.9 (115.0, 144.4)	**1.77 (1.53, 2.04)**
	Month 9	607	71.7 (65.4, 78.6)	355	73.1 (64.8, 82.4)	**0.98 (0.84, 1.14)**
DENV-4	**Month 4**	641	143.9 (132.8, 156.0)	367	137.4 (123.5, 152.9)	**1.05 (0.92, 1.20)**
	Month 9	607	64.0 (58.2, 70.4)	354	63.5 (56.0, 71.9)	**1.01 (0.86, 1.18)**

CI, confidence interval; GMR, geometric mean ratio; GMT, geometric mean titer; MNT_{50}, microneutralization test resulting in a titer reduction of at least 50%; n, number of participants with MNT_{50} results available; N, total number of participants.

(a) Adjusted GMTs, GMRs, and corresponding 95% CIs are calculated using an analysis of (co-)variance model with comparison group as factor and baseline MNT_{50} titer as covariate, as appropriate

For comparisons between the studies, a non-inferiority margin of the upper limit of the 95% CI <2 was applied. Non-inferiority was met for all comparisons, except for DENV-3 at Month 4 which was marginally missed (upper limit of 95% CI = 2.04).