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Additional Details:

Additional information regarding study design and methodology are available in previous reports from Biswal et al. [17, 22].

TAK-003 Construct

Takeda's tetravalent dengue vaccine candidate (TAK-003), is based on a live attenuated DENV-2 virus that provides the genetic backbone for all four of the vaccine viruses, which were originally designed and constructed by scientists at the Division of Vector-Borne Diseases of the Centers for Disease Control and Prevention. The DENV-2 strain (TDV-2) is based on an attenuated laboratory-derived virus, DEN-2 PDK-53. The other three virus strains (TDV-1, TDV-3, and TDV-4) are chimeras that were generated by replacing the pre-membrane and envelope genes of TDV-2 with those from wild-type DENV-1, DENV-3, and DENV-4 strains.

Trial vaccine and placebo

One 0.5 mL dose of TAK-003 contained approximately 3.6, 4.0, 4.6, and 5.1 log10 plaque forming units of TDV-1, TDV-2, TDV-3, and TDV-4, respectively. The placebo was a 0.5 mL injection of saline solution. Vaccine or placebo was administered subcutaneously into the upper arm. The lyophilized vaccine kits were kept at 2 – 8°C during shipping and storage, and reconstituted before administration in phosphate-buffered saline solution.

Randomization and blinding

Children who met the study entry criteria were randomly assigned 2 : 1 to receive two doses of TAK-003 or two doses of placebo given three months apart. Randomization was stratified by region and age (4 – 5 years, 6 – 11 years, and 12 – 16 years) using an interactive web response system and dynamic block assignment. Randomization information was generated by personnel authorized by the trial sponsor, and stored in a secure area accessible only to authorized personnel. A subset of 4000 of the 20,099 participants was randomly selected as described for additional safety and immunogenicity assessments. Investigators, participants, and their parents or guardians, and sponsor representatives advising on trial conduct were unaware of trial group assignments. One or more designated pharmacists or vaccine administrators were unmasked at each site, but had no role in the collection or assessment of participant safety data. These individuals accessed randomization information through a web portal. To maintain masking, medical writers and some sponsor-affiliated authors had access to group and anonymized individual-level study data. Other authors had access only to the data presented in this report. An independent data monitoring committee with responsibility for safety oversight had access to unmasked data on request.

Inclusion criteria

Subject eligibility was determined according to the following criteria: 1) the subject was aged 4 – 16 years, inclusive, at the time of randomization; 2) individuals were in good health at the time of entry into the trial as determined by medical history, physical examination (including vital signs), and the clinical judgment of the investigator; 3) the subject and/or the subject's parent/guardian signed and dated an assent/written informed consent form where applicable, and any required privacy

authorization prior to the initiation of any trial procedures, after the nature of the trial had been explained according to local regulatory requirements; and 4) individuals who could comply with trial procedures and were available for the duration of follow-up [as stated in study protocol].

Exclusion criteria

Any subject who met any of the following criteria did not qualify for entry into the trial: 1) febrile illness (temperature ≥ 38°C) or moderate or severe acute illness or infection at the time of randomization; 2) history of or any illness that, in the opinion of the investigator, might interfere with the results of the trial or pose an additional risk to the subject due to participation in the trial, including but not limited to [a] known hypersensitivity or allergy to any of the vaccine components, [b] female subjects (post-menarche) who were pregnant or breastfeeding, [c] individuals with any serious chronic or progressive disease according to the judgment of the investigator (e.g. neoplasm, insulin-dependent diabetes, cardiac, renal, or hepatic disease, neurologic or seizure disorders, or Guillain-Barré syndrome), [d] known or suspected impairment/alteration of immune function; 3) receipt of any other vaccine within 14 days (for inactivated vaccines) or 28 days (for live vaccines) prior to Day 1 or those planning to receive any vaccine within 28 days after Day 1; 4) participation in any clinical trial with another investigational product 30 days prior to Day 1 or intent to participate in another clinical trial at any time during the conduct of this trial; 5) previous participation in any clinical trial of a dengue candidate vaccine, or previous receipt of a dengue vaccine; 6) first degree relatives of individuals involved in trial conduct; 7) females of childbearing potential who were sexually active, and who had not used an acceptable contraceptive method for at least two months prior to Day 1; 8) females of childbearing potential who were sexually active, and who refused to use an acceptable contraceptive method up to six weeks post-second vaccination; 9) deprived of freedom by administrative or court order, or in an emergency setting, or hospitalized involuntarily; 10) current

alcohol abuse or drug addiction that may interfere with the subject's ability to comply with trial procedures; 11) identified as an employee of the investigator or trial center, with direct involvement in the proposed trial or other trials under the direction of that investigator or trial center. There may have been instances when individuals met all entry criteria except one that related to transient clinical circumstances (e.g. temperature elevation, or recent use of an excluded medication or vaccine). Under these circumstances, a subject may have been considered eligible for trial entry or first vaccination, as applicable, if the appropriate window for delay had passed, the inclusion/exclusion criteria had been rechecked, and if the subject was confirmed to be eligible [as stated in study protocol].

Statistical analysis

Efficacy endpoint analyses were performed on Per Protocol Set data (i.e. all participants without any major protocol violations; see data set definitions in Supplementary Material). The primary endpoint was efficacy of two TAK-003 doses in preventing VCD induced by any dengue serotype occurring from 30 days post-second vaccination until the end of Part 1. Secondary endpoints included efficacy against individual dengue serotypes, by baseline serostatus, and in prevention dengue leading to hospitalization and severe dengue in the timeframe of 30 days post-second vaccination to the end of Part 2. Vaccine efficacy is defined as $1 – (\lambda V / \lambda C)$, where λV and λC denote the hazard rates for the TAK-003 and placebo groups, respectively. Hazard ratios and corresponding 95% CIs were estimated using a Cox proportional hazard model with trial group as a factor, adjusted for age, and stratified by region. The primary vaccine efficacy objective was considered to be met if the lower bound of the 95% CI for vaccine efficacy was above 25%. The sample size calculation was based on the assumption of true vaccine efficacy of 60% and a background annual dengue incidence of 1%. Randomization of 20,100 participants in a 2 : 1 ratio (TAK-003 : placebo) could enable identification

of 120 VCD cases between 30 days post-second vaccination and the end of Part 1, providing at least 90% power to rule out a vaccine effect of 25% or more (with a two-sided significance level of 0.05). Secondary vaccine efficacy endpoints were evaluated on the Per Protocol Set using the same methods as the primary endpoint analysis with the aim to rule out vaccine efficacy of 0% in the assessment period 30 days post-second vaccination until the end of Part 2. Additional analyses were done on the Per Protocol Set, Safety Set, Full Analysis Set, and Safety and Immunogenicity subsets. All vaccine efficacy estimates in exploratory analyses were derived in a similar fashion as for the primary and secondary endpoints. Statistical analyses were performed using SAS software (version 9.3).

Analysis sets

Randomized Set: consists of all randomized subjects, regardless of whether or not any dose of the investigational product (vaccine or placebo) was received; subjects are summarized according to the investigational product to which they were assigned. Safety Set: consists of all randomized subjects who received at least one dose of investigational product (vaccine or placebo); subjects are summarized according to the investigational product received. Full Analysis Set (FAS): consists of all randomized subjects who received at least one dose of investigational product (vaccine or placebo); subjects are summarized according to the investigational product to which they were assigned. Full Analysis Set for Immunogenicity (FASI): consists of all randomized subjects in the FAS for whom a valid pre-injection and at least one valid post-injection blood sample were obtained for immunogenicity assessment. Per Protocol Set (PPS): consists of all subjects in the FAS with no major protocol violations. Per Protocol Set for Immunogenicity (PPSI): consists of all subjects in the FASI with no major protocol violations. Dry-Run Set: consists of all subjects who participated in the dry-run, whether randomized or not. Correlate of Protection Set: consists of all PPS subjects in the

subset and virologically-confirmed dengue fever cases. The categories of 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].

Procedures during active febrile surveillance (Part 1 and Part 2)

During active surveillance, participants presenting with febrile illness or clinically suspected dengue had blood samples taken in the acute (i.e. as soon as possible and preferably within five days of fever onset) and convalescent phases (i.e. 7 – 14 days after the acute sample). Testing included: quantitative serotype-specific RT-PCR; dengue NS1 / IgM / IgG ELISA; and hematocrit, liver enzyme (aspartate aminotransferase and alanine aminotransferase), and platelet counts. RT-PCR and NS1 ELISA assays were performed only on the acute sample. Febrile illnesses were evaluated clinically, and additional tests could be performed as per local standard of care.

Procedures during modified active febrile surveillance (Part 3)

Febrile surveillance in Part 3 of the study differed from Parts 1 and 2 in that a modified active surveillance is conducted to detect dengue cases of any severity based on the need for hospitalization. Participants with febrile illness are asked to return to the site for evaluation by the investigator. Blood samples are obtained from participants presenting with febrile illness not requiring hospitalization in order to confirm dengue infection by RT-PCR, unless there is an alternative laboratory-confirmed etiology. Participants with febrile illness requiring hospitalization

are evaluated as during the active surveillance periods (i.e., dry-run, and Parts 1 and 2 of the study). As with study Parts 1 and 2, the minimum frequency of participant contact in Part 3 is at least once per week.

Outcomes

For efficacy objectives, VCD was defined as febrile illness or illness clinically suspected to be dengue by the investigator with confirmation by positive serotype-specific RT-PCR. Only the first VCD case in a participant was included in the overall vaccine efficacy analysis. However, vaccine efficacy analysis by serotype included the first VCD case for a specific serotype in an individual participant. Specific criteria for hospitalization were not defined in the study protocol; participants were hospitalized according to the judgment of individual investigators. Severity of VCD was assessed using two approaches: (1) masked review by the Dengue Case Severity Adjudication Committee (DCAC) using predefined criteria, and (2) by a program developed by the study statisticians to analyze data according to the WHO 1997 dengue hemorrhagic fever criteria [23].

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.

Collection and reporting of SAEs

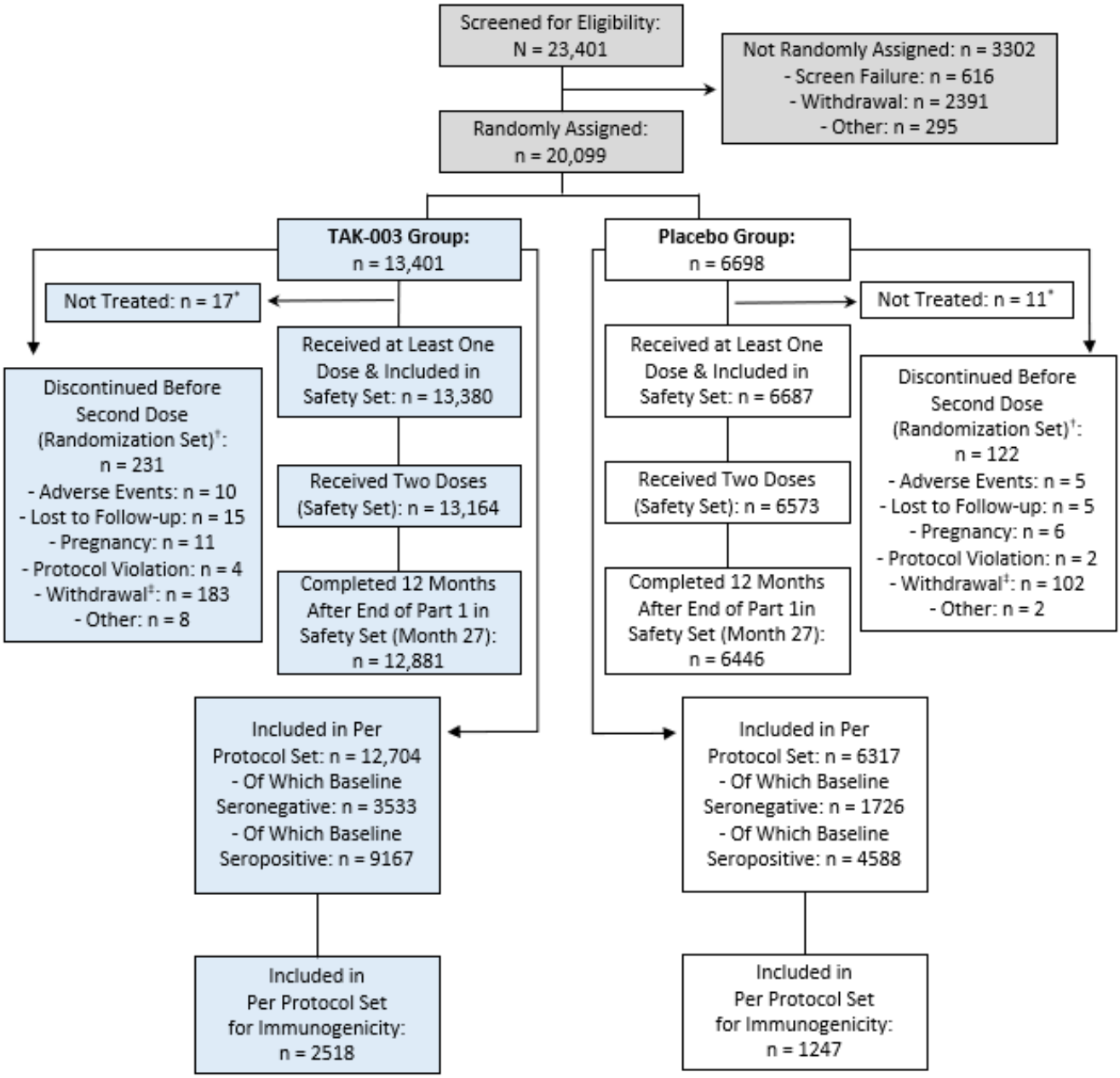
Collection of SAEs commenced from the time that the subject is first administered the investigational vaccine or placebo (Day 1 [Month 0]). Routine collection of all SAEs continued during Parts 1 and 2. During Part 3, investigators are required to report all deaths as well as SAEs assessed as related, or deemed relevant by the Investigator in the context of vaccine safety.

Supplementary Figure 1: Differences between active and modified active surveillance

	ACTIVE SURVEILLANCE (Dry-run; Part 1; Part 2)	**MODIFIED ACTIVE SURVEILLANCE** (Part 3)	
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 for a febrile illness that does not require hospitalization and has an alternate laboratory-confirmed etiology during Part 3

Supplementary Figure 2: Trial profile. Participants who did not receive a vaccine dose are included in the total numbers of participants who discontinued the trial before the second dose. Three participants in the vaccine group and two in the placebo group did not receive a second dose, but continued in the study. Four participants (three assigned to the vaccine group and one assigned to the placebo group) received both vaccine and placebo due to an administrative error; these participants were consequently excluded from the vaccine and placebo groups in the safety population. One participant assigned to the vaccine group received placebo; this participant was consequently included in the placebo group in the safety population. Participants had twelve months of follow-up after second dose at the time of completing Part 2 of the trial. Some data may differ from that previously published [17, 22] due to the inclusion of updated datasets.*Reasons not listed to preserve masking. †Includes non-vaccinated participants. ‡Withdrawn by participant or parent / legal guardian.



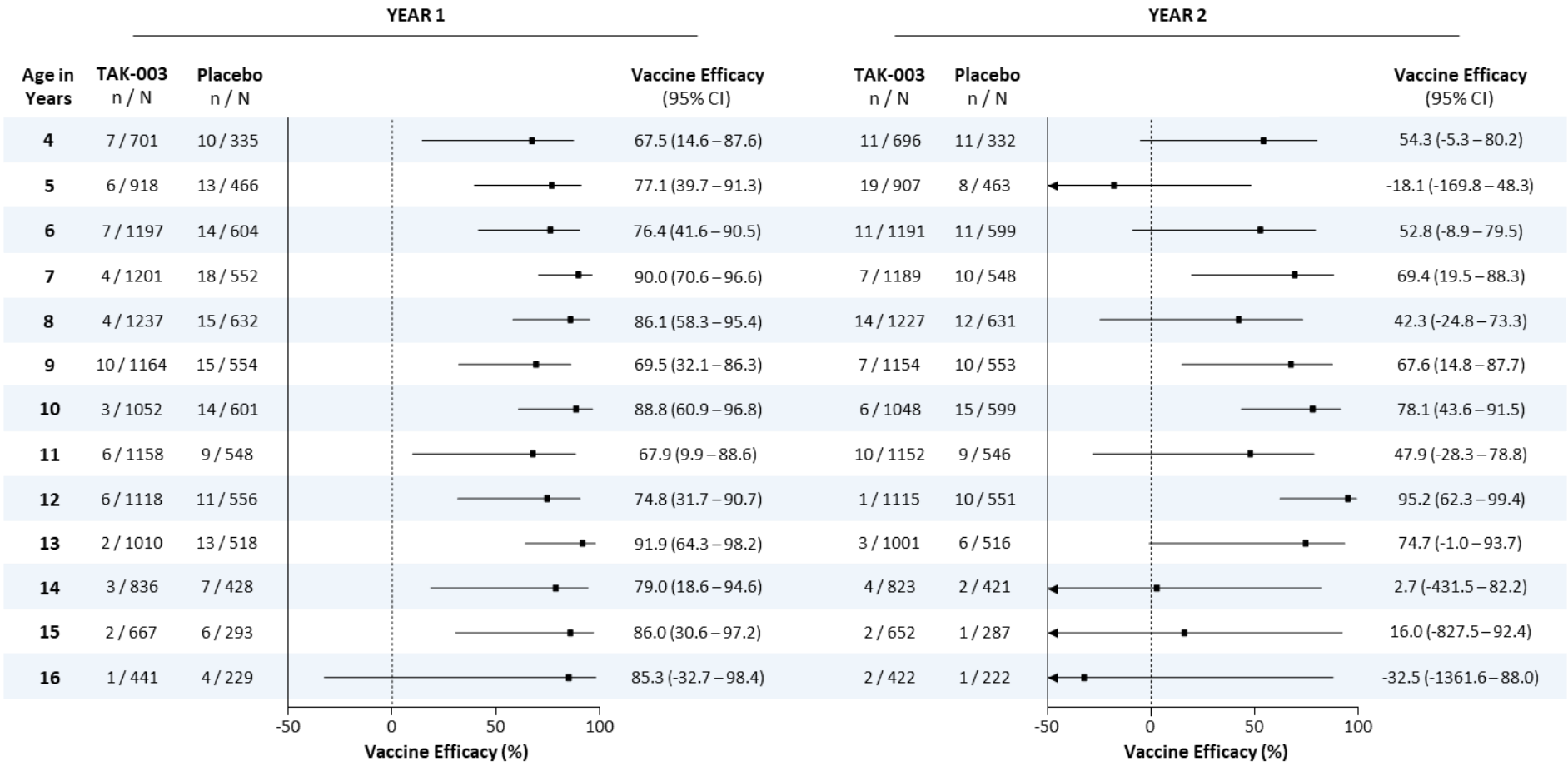
Supplementary Table 1: Number of participants experiencing serious adverse events (by system organ class and preferred term) occurring after any vaccination during 12 months of end of Part 1 (Month 16 to Month 27; Safety Set data). Four subjects received both TAK-003 and placebo and are therefore excluded from the data by treatment 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	**TAK-003** Number (%)	**Placebo** Number (%)	**Total** Number (%)
Number of Participants in the Safety Set	13,380	6687	20,071
Any Adverse Event	271 (2.0)	151 (2.3)	422 (2.1)
Infections & Infestations	158 (1.2)	91 (1.4)	249 (1.2)
Injury, Poisoning, & Procedural Complications	45 (0.3)	28 (0.4)	73 (0.4)
Gastrointestinal Disorders	16 (0.1)	12 (0.2)	28 (0.1)
Respiratory, Thoracic, & Mediastinal Disorders	13 (< 0.1)	7 (0.1)	20 (< 0.1)
Nervous System Disorders	12 (< 0.1)	5 (< 0.1)	17 (< 0.1)
Pregnancy, Puerperium, & Perinatal Conditions	7 (< 0.1)	3 (< 0.1)	10 (< 0.1)
Psychiatric Disorders	8 (< 0.1)	1 (< 0.1)	9 (< 0.1)
Blood & Lymphatic System Disorders	7 (< 0.1)	1 (< 0.1)	8 (< 0.1)
Musculoskeletal & Connective Tissue Disorders	5 (< 0.1)	1 (< 0.1)	6 (< 0.1)
Neoplasms	1 (< 0.1)	5 (< 0.1)	6 (< 0.1)
Social Circumstances	4 (< 0.1)	1 (< 0.1)	5 (< 0.1)
Reproductive System & Breast Disorders	2 (< 0.1)	2 (< 0.1)	4 (< 0.1)
Skin & Subcutaneous Tissue Disorders	3 (< 0.1)	1 (< 0.1)	4 (< 0.1)
Congenital, Familial, & Genetic Disorders	1 (< 0.1)	2 (< 0.1)	3 (< 0.1)
Immune System Disorders	2 (< 0.1)	1 (< 0.1)	3 (< 0.1)
Metabolism & Nutritional Disorders	1 (< 0.1)	1 (< 0.1)	2 (< 0.1)
General Disorders & Administration Site Conditions*	–	–	4 (< 0.1)
Hepatobiliary Disorders*	–	–	2 (< 0.1)
Renal & Urinary Disorders*	–	–	2 (< 0.1)
Eye Disorders*	–	–	1 (< 0.1)
Investigations*	–	–	1 (< 0.1)
Product Issues*	–	–	1 (< 0.1)
Vascular Disorders*	–	–	1 (< 0.1)

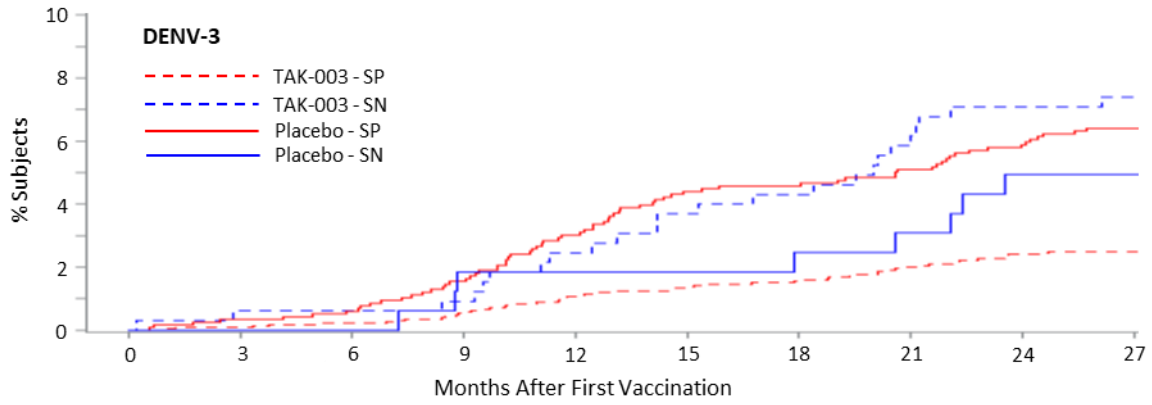
Supplementary Table 2: Serotype distribution (n / N) among cases of virologically-confirmed dengue (VCD; hospitalized VCD cases shown in parentheses) occurring between first vaccination and 12 months after end of Part 1 (Month 27 / Year 2 after second dose; Safety Set data). Pooled data for both TAK-003 and Placebo recipients.

	Total VCD Cases	DENV-1	DENV-2	DENV-3	DENV-4
All Participants	487 (111)	156 (25)	146 (67)	165 (17)	20 (2)
Seropositive	347 (77)	93 / 347 (16 / 77)	107 / 347 (47 / 77)	131 / 347 (12 / 77)	16 / 347 (2 / 77)
Seronegative	140 (34)	63 / 140 (9 / 34)	39 / 140 (20 / 34)	34 / 140 (5 / 34)	4 / 140 (0 / 34)
4 – 5 Years Old	94 (14)	28 / 94 (4 / 14)	10 / 94 (5 / 14)	50 / 94 (5 / 14)	6 / 94 (0 / 14)
6 – 11 Years Old	284 (66)	100 / 284 (16 / 66)	96 / 284 (40 / 66)	78 / 284 (9 / 66)	10 / 284 (1 / 66)
12 – 16 Years Old	109 (31)	28 / 109 (5 / 31)	40 / 109 (22 / 31)	37 / 109 (3 / 31)	4 / 109 (1 / 31)
Philippines	222 (19)	29 / 222 (2 / 19)	16 / 222 (1 / 19)	162 / 222 (16 / 19)	15 / 222 (0 / 19)
Sri Lanka	101 (64)	13 / 101 (5 / 64)	86 / 101 (58 / 64)	1 / 101 (0 / 64)	1 / 101 (1 / 64)
Thailand	43 (17)	22 / 43 (11 / 17)	16 / 43 (4 / 17)	2 / 43 (1 / 17)	3 / 43 (1 / 17)
Brazil	18 (2)	12 / 18 (2 / 2)	6 / 18 (0 / 2)	0 / 18 (0 / 2)	0 / 18 (0 / 2)
Colombia	41 (6)	38 / 41 (5 / 6)	2 / 41 (1 / 6)	0 / 41 (0 / 6)	1 / 41 (0 / 6)
Dominican Republic	7 (0)	7 / 7 (0)	0 / 7 (0)	0 / 7 (0)	0 / 7 (0)
Nicaragua	19 (3)	0 / 19 (0 / 3)	19 / 19 (3 / 3)	0 / 19 (0 / 3)	0 / 19 (0 / 3)
Panama	36 (0)	35 / 36 (0)	1 / 36 (0)	0 / 36 (0)	0 / 36 (0)

Supplementary Figure 3: Vaccine efficacy (95% CI) in prevention of virologically-confirmed dengue (VCD) fever occurring between 30 days post-second dose and end of Part 1 (Year 1 / Month 4 to Month 15, Per Protocol Set data), and over 12 months after end of Part 1 (Month 16 to Month 27, Per Protocol Set data). Forest plots show efficacy according to age (lower bound 95% CI values < minus 50 not shown on x-axis).



Supplementary Figure 4: Cumulative incidence of virologically-confirmed DENV-3 serotype infections occurring in the Philippines (Safety Set data), between first vaccination and 12 months after the end of Part 1 (Month 27 / Year 2 after second dose). SP, seropositive at baseline. SN, seronegative at baseline.



	Month 0	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24	Month 27
TAK-003 - SP	n = 2272	n = 2267	n = 2253	n = 2241	n = 2227	n = 2218	n = 2207	n = 2193	n = 2182	n = 1725
TAK-003 - SN	n = 327	n = 324	n = 324	n = 322	n = 317	n = 312	n = 310	n = 305	n = 301	n = 240
Placebo - SP	n = 1164	n = 1158	n = 1153	n = 1141	n = 1123	n = 1103	n = 1098	n = 1091	n = 1081	n = 828
Placebo - SN	n = 163	n = 163	n = 162	n = 159	n = 159	n = 159	n = 158	n = 157	n = 154	n = 126

Supplementary Table 3: Characteristics of severe virologically-confirmed dengue (VCD) cases and dengue hemorrhagic fever (DHF) cases occurring from first dose administration to study Year 2 (Safety Set data). Pooled data for both TAK-003 and Placebo recipients.

	Time of Onset[†]	Age in Years*	Baseline Serostatus	Dengue Serotype	Clinical Diagnosis
Severe VCD	Year 1	9	Positive	DENV-3	DHF
Severe VCD	Year 1	8	Negative	DENV-3	Dengue Fever
Severe VCD & DHF	Year 2	5	Negative	DENV-3	DHF
Severe VCD	Year 2	9	Positive	DENV-2	Dengue Fever
Severe VCD[‡]	Year 2	4	Positive	DENV-3	DHF
DHF	Year 1	12	Positive	DENV-3	DHF
DHF	Year 1	12	Negative	DENV-3	DHF
DHF	Year 1	16	Positive	DENV-2	DHF
DHF	Year 1	9	Positive	DENV-2	DHF
DHF	Year 1	16	Positive	DENV-2	DHF
DHF	Year 2	8	Positive	DENV-1	DHF
DHF	Year 2	6	Positive	DENV-1	DHF
DHF[§]	Year 2	8	Positive	DENV-2	Dengue Fever
DHF	Year 2	5	Negative	DENV-3	DHF
DHF	Year 2	12	Positive	DENV-1	DHF

VCD, virologically-confirmed dengue; DHF, dengue hemorrhagic fever; *age at time of randomization; [†]time of onset after last vaccination; [‡]participant did not receive second dose, and data excluded from Per Protocol Set vaccine efficacy evaluation; [§]participant did not require hospitalization

Supplementary Table 4: Clinical signs and symptoms of virologically-confirmed dengue (VCD) cases occurring between first vaccination and 12 months after the end of Part 1 (Month 27 / Year 2 after second dose; Safety Set data).

	TAK-003 Seropositive (n = 9663)	**Placebo Seropositive** (n = 4854)	**TAK-003 Seronegative** (n = 3714)	**Placebo Seronegative** (n = 1832)
Number of VCD Cases	119	228	56	84
Duration of Febrile Illness (Days; Median / Mean; 95% CI)*	5.0 / 6.2 (5.6 – 6.8)	6.0 / 6.5 (6.0 – 6.9)	6.0 / 6.9 (5.8 – 7.9)	6.0 / 7.0 (6.0 – 8.0)
Duration of Fever (Days; Median / Mean; 95% CI)	4.0 / 3.9 (3.6 – 4.1)	5.0 / 4.6 (4.3 – 4.8)	4.0 / 4.0 (3.6 – 4.5)	5.0 / 5.0 (4.5 – 5.4)
Number of Hospitalized VCD Cases	13	64	7	27
Duration of Hospitalization (Days; Median / Mean; 95% CI)	3.0 / 3.6 (2.9 – 4.3)	5.0 / 5.3 (4.8 – 5.8)	6.0 / 6.4 (5.1 – 7.7)	5.0 / 5.0 (4.3 – 5.6)
Evidence of Bleeding (%, n / N)	4.2% (5 / 119)	8.3% (19 / 228)	5.4% (3 / 56)	7.1% (6 / 84)
Plasma Leakage (%, n / N)	0.8% (1 / 119)	6.1% (14 / 228)	5.4% (3 / 56)	3.6% (3 / 84)
Hematocrit Increase ≥ 20% (%, n / N)†	3.1% (2 / 64)	13.0% (18 / 138)	7.1% (2 / 28)	3.3% (2 / 61)
Platelet Count ≤ 100 x 10^9 / L (%, n / N)‡	4.7% (5 / 107)	24.8% (54 / 218)	8.2% (4 / 49)	14.3% (11 / 77)
Platelet Count ≤ 50 x 10^9 / L (%, n / N)‡	1.9% (2 / 107)	12.4% (27 / 218)	4.1% (2 / 49)	5.2% (4 / 77)
ALT or AST ≥ 1000 U / L (%, n / N)‡	0% (0 / 96)	0% (0 / 205)	0% (0 / 44)	0% (0 / 75)
Signs of Circulatory Failure (Any) (%, n / N)	0% (0 / 119)	0.9% (2 / 228)	1.8% (1 / 56)	0% (0 / 84)
Reduced Pulse Pressure (%, n / N)	0% (0 / 119)	0.9% (2 / 228)	0% (0 / 56)	0% (0 / 84)
Hypotensive Shock (%, n / N)	0% (0 / 119)	0.4% (1 / 228)	1.8% (1 / 56)	0% (0 / 84)

VCD, virologically-confirmed dengue; ALT, alanine aminotransferase; AST, aspartate aminotransferase; *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); †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 DENV-3 serotype infections occurring between first vaccination and 12 months after the end of Part 1 (Month 27 / Year 2; Safety Set data).

	TAK-003 Seropositive (n = 9663)	**Placebo Seropositive** (n = 4854)	**TAK-003 Seronegative** (n = 3714)	**Placebo Seronegative** (n = 1832)
Number of DENV-3 VCD Cases	57	74	25	9
Duration of Febrile Illness (Days; Median / Mean; 95% CI)*	5.0 / 6.3 (5.3 – 7.4)	6.0 / 6.9 (6.0 – 7.8)	6.0 / 7.6 (5.8 – 9.5)	5.0 / 6.0 (3.8 – 8.2)
Duration of Fever (Days; Median / Mean; 95% CI)	4.0 / 3.8 (3.4 – 4.1)	4.0 / 4.3 (3.9 – 4.8)	3.0 / 3.6 (3.1 – 4.1)	5.0 / 4.4 (2.9 – 6.0)
Number of Hospitalized DENV-3 VCD Cases	4	8	4	1
Duration of Hospitalization (Days; Median / Mean; 95% CI)	5.0 / 4.8 (4.0 – 5.5)	6.0 / 6.6 (4.9 – 8.4)	7.0 / 7.3 (5.2 – 9.3)	5.0 / 5.0 (–)
Evidence of Bleeding (%, n / N)	3.5% (2 / 57)	4.1% (3 / 74)	8.0% (2 / 25)	22.2% (2 / 9)
Plasma Leakage (%, n / N)	0% (0 / 57)	0% (0 / 74)	12.0% (3 / 25)	11.1% (1 / 9)
Hematocrit Increase ≥ 20% (%, n / N)†	3.1% (1 / 32)	20.7% (6 / 29)	13.3% (2 / 15)	20% (1 / 5)
Platelet Count ≤ 100 x 10^9 / L (%, n / N)‡	5.5% (3 / 55)	11.1% (8 / 72)	13.0% (3 / 23)	14.3% (1 / 7)
Platelet Count ≤ 50 x 10^9 / L (%, n / N)‡	1.8% (1 / 55)	4.2% (3 / 72)	4.3% (1 / 23)	0% (0 / 7)
ALT or AST ≥ 1000 U / L (%, n / N)‡	0% (0 / 47)	0% (0 / 62)	0% (0 / 21)	0% (0 / 6)
Signs of Circulatory Failure (Any) (%, n / N)	0% (0 / 57)	1.4% (1 / 74)	4% (1 / 25)	0% (0 / 9)
Reduced Pulse Pressure (%, n / N)	0% (0 / 57)	1.4% (1 / 74)	0% (0 / 25)	0% (0 / 9)
Hypotensive Shock (%, n / N)	0% (0 / 57)	0% (0 / 74)	4% (1 / 25)	0% (0 / 9)

VCD, virologically-confirmed dengue; ALT, alanine aminotransferase; AST, aspartate aminotransferase; *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); †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 DENV-3 VCD cases with available data for specific parameter)

Supplementary Table 6: Geometric mean titers (95% CI) by dengue serotype (Per Protocol Set for Immunogenicity data). Data rounded to nearest whole number, except values < 10 which are presented to one decimal place. 'n' refers to number of participants in the analysis set. Number of participants evaluated at each timepoint may vary. Some data may differ from that previously published [17, 22] due to the inclusion of updated datasets and a change in imputation rule when MNT values are between lower limit of detection (i.e., 10) and the lower limit of quantification.

	TAK-003 Seropositive (n = 1816)	**Placebo Seropositive** (n = 902)	**TAK-003 Seronegative** (n = 702)	**Placebo Seronegative** (n = 345)
DENV-1				
Month 0	411 (366 – 462)	445 (378 – 525)	5.0 (5.0 – 5.0)	5.0 (5.0 – 5.0)
Month 1	2404 (2204 – 2622)	430 (361 – 512)	118 (106 – 131)	5.8 (5.3 – 6.3)
Month 3	1947 (1793 – 2114)	410 (350 – 482)	91 (82 – 102)	5.9 (5.4 – 6.3)
Month 4	2115 (1957 – 2286)	454 (383 – 536)	184 (169 – 201)	6.3 (5.7 – 7.0)
Month 9	1446 (1328 – 1573)	415 (350 – 492)	88 (79 – 98)	6.3 (5.8 – 6.9)
Month 15	1250 (1145 – 1365)	453 (382 – 537)	77 (69 – 87)	6.9 (6.1 – 7.8)
Month 27	1137 (1035 – 1249)	491 (411 – 588)	73 (63 – 84)	8.7 (7.2 – 11)
DENV-2				
Month 0	753 (681 – 833)	805 (699 – 927)	5.0 (5.0 – 5.0)	5.0 (5.0 – 5.0)
Month 1	6696 (6300 – 7116)	746 (638 – 873)	6277 (5648 – 6977)	6.6 (6.0 – 7.3)
Month 3	4826 (4571 – 5095)	725 (625 – 840)	1682 (1543 – 1833)	7.1 (6.3 – 8.0)
Month 4	4897 (4646 – 5163)	767 (656 – 897)	1730 (1614 – 1855)	7.8 (6.8 – 8.9)
Month 9	3691 (3496 – 3898)	778 (667 – 907)	929 (855 – 1009)	8.9 (7.5 – 10)
Month 15	2999 (2836 – 3170)	745 (636 – 873)	656 (601 – 717)	8.5 (7.2 – 10)
Month 27	1657 (1550 – 1771)	561 (479 – 657)	356 (320 – 397)	9.8 (7.9 – 12)
DENV-3				
Month 0	358 (321 – 398)	356 (305 – 416)	5.0 (5.0 – 5.0)	5.0 (5.0 – 5.0)
Month 1	2254 (2093 – 2428)	350 (299 – 410)	195 (174 – 218)	5.5 (5.2 – 5.9)
Month 3	1563 (1453 – 1682)	322 (277 – 374)	94 (85 – 104)	5.5 (5.1 – 5.9)
Month 4	1761 (1646 – 1884)	354 (302 – 415)	228 (212 – 246)	6.0 (5.4 – 6.6)
Month 9	1088 (1008 – 1174)	308 (262 – 361)	72 (66 – 78)	6.4 (5.7 – 7.1)
Month 15	803 (742 – 870)	284 (242 – 333)	54 (49 – 59)	6.3 (5.8 – 6.9)
Month 27	725 (666 – 791)	309 (262 – 364)	55 (48 – 62)	7.6 (6.6 – 8.8)
DENV-4				
Month 0	218 (198 – 241)	234 (203 – 270)	5.0 (5.0 – 5.0)	5.0 (5.0 – 5.0)
Month 1	1306 (1224 – 1393)	222 (192 – 258)	111 (98 – 126)	5.4 (5.0 – 5.7)
Month 3	1002 (940 – 1069)	215 (187 – 248)	63 (57 – 70)	5.5 (5.1 – 5.9)
Month 4	1129 (1066 – 1196)	242 (208 – 280)	144 (134 – 155)	5.8 (5.4 – 6.4)
Month 9	778 (730 – 830)	229 (198 – 266)	64 (59 – 70)	6.2 (5.6 – 6.9)
Month 15	818 (766 – 874)	293 (252 – 340)	64 (58 – 71)	6.4 (5.8 – 7.1)
Month 27	636 (592 – 682)	264 (228 – 307)	56 (50 – 63)	7.5 (6.5 – 8.6)

Supplementary Table 7: Seropositivity rates (percentages of evaluated participants, 95% CI) by dengue serotype (Per Protocol Set for Immunogenicity data). Data rounded to nearest whole number, except values < 10 which are presented to one decimal place. 'n' refers to number of participants in the analysis set. Number of participants evaluated at each timepoint may vary. Some data may differ from that previously published [17, 22] due to the inclusion of updated datasets and a change in imputation rule when MNT values are between lower limit of detection (i.e., 10) and the lower limit of quantification.

	TAK-003 Seropositive (n = 1816)	**Placebo Seropositive** (n = 902)	**TAK-003 Seronegative** (n = 702)	**Placebo Seronegative** (n = 345)
DENV-1				
Month 0	89 (88 – 91)	91 (89 – 92)	0 (0 – 0.5)	0 (0 – 1.1)
Month 1	100 (99 – 100)	89 (86 – 91)	94 (92 – 96)	4.9 (2.8 – 7.8)
Month 3	99 (99 – 100)	90 (88 – 92)	92 (89 – 94)	6.1 (3.8 – 9.2)
Month 4	100 (100 – 100)	90 (88 – 92)	100 (99 – 100)	8.3 (5.5 – 12)
Month 9	100 (99 – 100)	90 (88 – 92)	95 (93 – 97)	9.0 (6.0 – 13)
Month 15	99 (99 – 100)	90 (88 – 92)	93 (91 – 95)	10 (7.1 – 14)
Month 27	99 (99 – 100)	91 (88 – 93)	90 (88 – 93)	15 (11 – 20)
DENV-2				
Month 0	97 (96 – 97)	97 (96 – 98)	0 (0 – 0.5)	0 (0 – 1.1)
Month 1	100 (100 – 100)	93 (91 – 95)	99 (97 – 99)	11 (7.5 – 15)
Month 3	100 (100 – 100)	94 (92 – 95)	99 (98 – 100)	12 (8.9 – 16)
Month 4	100 (100 – 100)	94 (92 – 95)	100 (99 – 100)	15 (11 – 19)
Month 9	100 (100 – 100)	95 (93 – 96)	100 (99 – 100)	18 (14 – 23)
Month 15	100 (100 – 100)	93 (91 – 95)	100 (99 – 100)	13 (9.5 – 17)
Month 27	100 (100 – 100)	94 (91 – 95)	100 (99 – 100)	15 (11 – 20)
DENV-3				
Month 0	88 (87 – 90)	88 (86 – 90)	0 (0 – 0.5)	0 (0 – 1.1)
Month 1	100 (99 – 100)	88 (85 – 90)	96 (94 – 97)	4.0 (2.1 – 6.7)
Month 3	100 (99 – 100)	87 (85 – 89)	94 (93 – 96)	2.0 (0.8 – 4.1)
Month 4	100 (100 – 100)	88 (86 – 90)	100 (99 – 100)	5.1 (2.9 – 8.2)
Month 9	100 (99 – 100)	87 (85 – 89)	96 (95 – 98)	7.7 (4.9 – 11)
Month 15	100 (99 – 100)	86 (84 – 89)	93 (90 – 95)	8.3 (5.5 – 12)
Month 27	99 (99 – 100)	88 (86 – 91)	92 (89 – 94)	13 (8.9 – 17)
DENV-4				
Month 0	88 (87 – 90)	87 (85 – 90)	0 (0 – 0.5)	0 (0 – 1.1)
Month 1	100 (99 – 100)	87 (84 – 89)	91 (88 – 93)	1.8 (0.7 – 3.9)
Month 3	99 (99 – 100)	87 (85 – 89)	92 (90 – 94)	2.9 (1.4 – 5.3)
Month 4	100 (100 – 100)	88 (86 – 90)	100 (99 – 100)	4.8 (2.7 – 7.8)
Month 9	100 (99 – 100)	88 (85 – 90)	97 (95 – 98)	6.3 (3.9 – 9.7)
Month 15	100 (99 – 100)	89 (86 – 91)	95 (93 – 97)	8.0 (5.2 – 12)
Month 27	100 (99 – 100)	90 (87 – 92)	94 (92 – 96)	13 (9.2 – 18)

Supplementary Table 8: Geometric mean titers (95% CI) by dengue serotype and age group in TAK-003 recipients seronegative at baseline (Per Protocol Set for Immunogenicity data). Data rounded to nearest whole number except values < 10 which are presented to one decimal place. 'n' refers to number of seronegative TAK-003 recipients in the analysis set. Numbers of participants evaluated at each timepoint may vary.

	4 – 5 Years Old (n = 132)	**6 – 11 Years Old** (n = 433)	**12 – 16 Years Old** (n = 137)
DENV-1			
Month 0	5.0 (5.0 – 5.0)	5.0 (5.0 – 5.0)	5.0 (5.0 – 5.0)
Month 1	117 (92 – 149)	124 (108 – 141)	103 (81 – 131)
Month 3	92 (71 – 120)	87 (76 – 99)	104 (78 – 139)
Month 4	233 (191 – 284)	173 (155 – 194)	177 (145 – 217)
Month 9	97 (76 – 125)	84 (74 – 96)	91 (69 – 119)
Month 15	88 (66 – 117)	71 (62 – 81)	91 (67 – 123)
Month 27	83 (63 – 110)	66 (55 – 79)	88 (57 – 135)
DENV-2			
Month 0	5.0 (5.0 – 5.0)	5.0 (5.0 – 5.0)	5.0 (5.0 – 5.0)
Month 1	5799 (4777 – 7040)	6180 (5400 – 7074)	7086 (5368 – 9353)
Month 3	1273 (1051 – 1542)	1657 (1484 – 1850)	2306 (1908 – 2786)
Month 4	1490 (1298 – 1711)	1678 (1533 – 1837)	2209 (1876 – 2601)
Month 9	747 (619 – 901)	892 (803 – 992)	1287 (1074 – 1544)
Month 15	524 (426 – 644)	634 (570 – 705)	905 (721 – 1136)
Month 27	310 (233 – 413)	334 (294 – 379)	519 (403 – 668)
DENV-3			
Month 0	5.0 (5.0 – 5.0)	5.0 (5.0 – 5.0)	5.0 (5.0 – 5.0)
Month 1	164 (124 – 216)	193 (167 – 223)	234 (181 – 302)
Month 3	85 (68 – 107)	91 (81 – 103)	114 (88 – 146)
Month 4	224 (191 – 262)	235 (214 – 258)	211 (174 – 256)
Month 9	60 (50 – 72)	74 (67 – 82)	77 (61 – 98)
Month 15	52 (40 – 66)	51 (46 – 57)	65 (50 – 85)
Month 27	56 (43 – 73)	50 (44 – 58)	69 (50 – 97)
DENV-4			
Month 0	5.0 (5.0 – 5.0)	5.0 (5.0 – 5.0)	5.0 (5.0 – 5.0)
Month 1	92 (69 – 123)	109 (93 – 127)	139 (101 – 191)
Month 3	55 (43 – 70)	62 (55 – 70)	78 (60 – 101)
Month 4	149 (125 – 178)	145 (133 – 159)	135 (112 – 164)
Month 9	65 (53 – 80)	63 (57 – 70)	65 (51 – 82)
Month 15	62 (48 – 80)	64 (57 – 71)	67 (51 – 89)
Month 27	62 (47 – 81)	52 (46 – 59)	66 (47 – 94)

Supplementary Table 9: Seropositivity rates (percentages of evaluated participants, 95% CI) by dengue serotype and age group in TAK-003 recipients seronegative at baseline (Per Protocol Set for Immunogenicity data). Data rounded to nearest whole number except values < 10 which are presented to one decimal place. 'n' refers to number of seronegative TAK-003 recipients in the analysis set. Numbers of participants evaluated at each timepoint may vary.

	4 – 5 Years Old (n = 132)	**6 – 11 Years Old** (n = 433)	**12 – 16 Years Old** (n = 137)
DENV-1			
Month 0	0 (0 – 2.8)	0 (0 – 0.8)	0 (0 – 2.7)
Month 1	94 (89 – 98)	95 (93 – 97)	90 (84 – 95)
Month 3	89 (83 – 94)	93 (90 – 95)	89 (83 – 94)
Month 4	99 (96 – 100)	100 (98 – 100)	100 (97 – 100)
Month 9	97 (91 – 99)	95 (93 – 97)	93 (87 – 97)
Month 15	95 (88 – 98)	93 (90 – 95)	93 (87 – 97)
Month 27	94 (87 – 98)	90 (86 – 93)	89 (80 – 94)
DENV-2			
Month 0	0 (0 – 2.8)	0 (0 – 0.8)	0 (0 – 2.7)
Month 1	100 (97 – 100)	99 (97 – 100)	97 (93 – 99)
Month 3	99 (95 – 100)	99 (98 – 100)	99 (96 – 100)
Month 4	100 (97 – 100)	100 (99 – 100)	100 (97 – 100)
Month 9	100 (97 – 100)	100 (99 – 100)	100 (97 – 100)
Month 15	100 (97 – 100)	100 (99 – 100)	100 (97 – 100)
Month 27	99 (94 – 100)	100 (99 – 100)	100 (96 – 100)
DENV-3			
Month 0	0 (0 – 2.8)	0 (0 – 0.8)	0 (0 – 2.7)
Month 1	94 (89 – 98)	97 (94 – 98)	96 (91 – 99)
Month 3	95 (89 – 98)	94 (92 – 96)	94 (89 – 97)
Month 4	100 (97 – 100)	100 (99 – 100)	100 (97 – 100)
Month 9	95 (89 – 98)	97 (95 – 99)	96 (91 – 99)
Month 15	90 (83 – 95)	93 (90 – 96)	93 (87 – 97)
Month 27	93 (85 – 97)	92 (88 – 95)	91 (83 – 96)
DENV-4			
Month 0	0 (0 – 2.8)	0 (0 – 0.8)	0 (0 – 2.7)
Month 1	90 (84 – 95)	91 (88 – 94)	88 (81 – 93)
Month 3	89 (83 – 94)	93 (90 – 95)	91 (85 – 95)
Month 4	99 (96 – 100)	100 (99 – 100)	100 (97 – 100)
Month 9	97 (91 – 99)	98 (96 – 99)	94 (89 – 98)
Month 15	93 (86 – 97)	97 (94 – 98)	92 (86 – 96)
Month 27	93 (85 – 97)	95 (92 – 97)	92 (84 – 97)