Long-term efficacy and safety of a tetravalent dengue vaccine (TAK-003): 4·5-year results from a phase 3, randomised, double-blind, placebo-controlled trial

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Summary

Background About half of the world's population lives in dengue-endemic areas. We aimed to evaluate the long-term efficacy and safety of two doses of the tetravalent dengue vaccine TAK-003 in preventing symptomatic dengue disease of any severity and due to any dengue virus (DENV) serotypes in children and adolescents.

Methods In this ongoing double-blind, randomised, placebo-controlled trial, we enrolled healthy participants aged 4–16 years at 26 medical and research centres across eight dengue-endemic countries (Brazil, Colombia, Dominican Republic, Nicaragua, Panama, Philippines, Sri Lanka, and Thailand). The main exclusion criteria were febrile illness (body temperature ≥38°C) at the time of randomisation, hypersensitivity or allergy to any of the vaccine components, pregnancy or breastfeeding, serious chronic or progressive disease, impaired or altered immune function, and previous receipt of a dengue vaccine. Participants were randomly assigned 2:1 (stratified by age and region) using an interactive web response system and dynamic block assignment to receive two subcutaneous doses of TAK-003 or placebo 3 months apart. Investigators, participants, and their parents or legal guardians were blinded to group assignments. Active febrile illness surveillance and RT-PCR testing of febrile illness episodes were performed for identification of virologically confirmed dengue. Efficacy outcomes were assessed in the safety analysis set (all randomly assigned participants who received ≥1 dose) and the per protocol set (all participants who had no major protocol violations), and included cumulative vaccine efficacy from first vaccination to approximately 4·5 years after the second vaccination. Serious adverse events were monitored throughout. This study is registered with ClinicalTrials.gov, NCT02747927.

Findings Between Sept 7, 2016, and March 31, 2017, 20 099 participants were randomly assigned (TAK-003, n=13 401; placebo, n=6698). 20 071 participants (10 142 [50·5%] males; 9929 [49·5%] females; safety set) received TAK-003 or placebo, with 18 257 (91·0%) completing approximately 4·5 years of follow-up after the second vaccination (TAK-003, 12 177/13 380; placebo, 6080/6687). Overall, 1007 (placebo: 560; TAK-003: 447) of 27 684 febrile illnesses reported were virologically confirmed dengue, with 188 cases (placebo: 142; TAK-003: 46) requiring hospitalisation. Cumulative vaccine efficacy was 61·2% (95% CI 56·0–65·8) against virologically confirmed dengue and 84·1% (77·8–88·6) against hospitalised virologically confirmed dengue; corresponding efficacies were 53·5% (41·6–62·9) and 79·3% (63·5–88·2) in baseline seronegative participants (safety set). In an exploratory analysis, vaccine efficacy was shown against all four serotypes in baseline seropositive participants. In baseline seronegative participants, vaccine efficacy was shown against DENV-1 and DENV-2 but was not observed against DENV-3 and low incidence precluded evaluation against DENV-4. During part 3 of the trial (approximately 22–57 months after the first vaccination), serious adverse events were reported for 664 (5·0%) of 13 380 TAK-003 recipients and 396 (5·9%) of 6687 placebo recipients; 17 deaths (6 in the placebo group and 11 in the TAK-003 group) were reported, none were considered study-vaccine related.

Interpretation TAK-003 demonstrated long-term efficacy and safety against all four DENV serotypes in previously exposed individuals and against DENV-1 and DENV-2 in dengue-naive individuals.

Funding Takeda Vaccines.

Introduction

Mosquito-borne infections such as dengue are an increasing threat to worldwide health, with the range of mosquito vectors expanding from tropical and subtropical regions into temperate and higher elevation areas.[1] In the past two decades, the number of dengue cases reported to WHO has increased eight-fold, partly related to changes in national recording and reporting practices.[2]

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For the Portuguese translation of the abstract see Online for appendix 1

For the Spanish translation of the abstract see Online for appendix 2

For the plain language summary see Online for appendix 3

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Research in context

Evidence before this study

The PubMed database was searched for reports published from database inception until June 12, 2023, using the following search terms: "dengue vaccine", "dengue vaccine clinical trial", and "dengue vaccine phase 1, 2, and 3". Information was also sought from ClinicalTrials.gov, and national and international public health agencies. There were no licensed vaccines against dengue when this phase 3 study was conceived. The dengue vaccine CYD-TDV (Sanofi Pasteur) has since been approved for use in a three-dose vaccination schedule in children and adults with previous dengue infection in several countries. Other vaccine candidates to reach phase 3 clinical development include TV003/Butantan-DV and TAK-003. 2-year follow-up data from an ongoing phase 3 trial (NCT02406729) of a single dose of TV003/Butantan-DV showed 79·6% overall efficacy against dengue disease in participants aged 2–59 years, with the caveat that no efficacy data against dengue virus (DENV)-3 and DENV-4 could be obtained since these viruses were not widely circulating in Brazil where the trial was conducted. The long-term efficacy and safety of TAK-003 in healthy individuals aged 4–16 years living in eight dengue-endemic countries across Asia and Latin America has been assessed in a phase 3 trial. Primary, secondary, and exploratory endpoint data were reported previously, and showed that two doses of TAK-003 had a favourable safety profile in this population and were efficacious up to 3 years after administration of the primary vaccine series. TAK-003 has been approved for use in individuals with and without previous dengue infection in some endemic and non-endemic countries.

Added value of this study

The long-term data presented herein show that TAK-003 is efficacious against symptomatic dengue disease in healthy children and adolescents aged 4–16 years living in eight dengue-endemic countries, with over 4 years of active febrile illness surveillance. Cumulative vaccine efficacy against virologically confirmed dengue was 64·2% in dengue-exposed participants and 53·5% in dengue-naive participants from first dose up to 4·5 years after the second dose. Efficacy was demonstrated against all DENV serotypes (DENV-1, DENV-2, DENV-3, and DENV-4) in dengue-exposed participants, and against DENV-1 and DENV-2 in dengue-naive participants. In dengue-naive participants, although data suggest a lack of efficacy against DENV-3, and low incidence precludes an assessment of efficacy against DENV-4 (virologically confirmed dengue, n=15 cases; hospitalised virologically confirmed dengue, n=1 case), the totality of data did not indicate increased disease severity in the 4·5 years of follow-up. Consequently, these uncertainties and any potential risks need to be considered in the overall benefit-risk assessment. Vaccine efficacy against virologically confirmed dengue was also demonstrated during year 4 of the trial, irrespective of serostatus. Cumulative vaccine efficacy against virologically confirmed dengue requiring hospitalisation was high at 85·9% and 79·3% in dengue-exposed and dengue-naive participants, respectively. TAK-003 also demonstrated a favourable safety profile during part 3 of the trial in this population.

Implications of all the available evidence

The global burden of dengue disease is high and growing. The long-term efficacy and safety data presented in this report demonstrates potential for TAK-003 to help combat the risk of dengue disease posed to those living in, or travelling to, dengue-endemic areas.

Dengue is caused by dengue virus (DENV)-1, DENV-2, DENV-3, or DENV-4 and all four serotypes now co-circulate in many endemic areas.[3] In 2012, a global strategy was formulated to reduce the burden of dengue by 2020.[4] Despite this strategy, 2019 saw the largest number of dengue cases globally. Although dengue disease burden appeared to decrease in 2020 and 2021,[5] which might have been partly related to reduced detection and reporting during the COVID-19 pandemic rather than solely to changes in disease transmission,[6] a trend towards increasing burden of dengue disease was again observed in 2022, for example, the number of dengue cases reported in the Americas rose from 1·2 million in 2021 to 2·8 million in 2022.[7] Even with decreases in disease burden in many countries, the diagnosis and treatment of dengue place immense pressure on health-care services in underserved regions and those already overwhelmed by COVID-19, particularly in urban high-risk areas for both diseases.[6]

Current dengue control strategies focus mainly on vector control, but this alone can be ineffective or insufficient in the long term.[8] Vector control and immunisation have the potential to complement each other and might produce synergistic results for the prevention of dengue. The complexity of dengue pathology, together with the need to develop a vaccine that can be efficacious in both dengue-naive and previously exposed individuals against all four serotypes simultaneously, has hampered vaccine development efforts.[9] Although the first tetravalent dengue vaccine, CYD-TDV (Sanofi Pasteur, Lyon, France), has been licensed in many countries, its indication is currently limited to individuals with evidence of previous DENV infection, owing to an elevated risk of severe disease and hospitalisation following a subsequent DENV infection in dengue-naive recipients.[10,11] Pre-vaccination screening of vaccine recipients can be costly, is challenging in resource-limited situations, and is currently limited by the absence of a single standardised test with high sensitivity and specificity.[12]

TAK-003 (Takeda Vaccines, Cambridge, MA, USA), a live-attenuated tetravalent dengue vaccine based on

a DENV-2 backbone,[13] was evaluated in a long-term efficacy trial in children and adolescents living in dengue-endemic areas of Asia and Latin America (NCT02747927), for which follow-up after a primary two-dose series has been completed. The study met its primary endpoint 1 year after receipt of the primary series, administered at months 0 and 3, with overall vaccine efficacy against virologically confirmed dengue of 80·2% (95% CI 73·3–85·3).[14] 18 months after vaccination, efficacy was 66·2% (49·1–77·5) in dengue-naive and 76·1% (68·5–81·9) in dengue-exposed recipients, and overall efficacy against hospitalised dengue was 90·4% (82·6–94·7).[15] Efficacy varied by individual serotypes. Some waning of vaccine efficacy against virologically confirmed dengue was observed through 3 years after vaccination (overall vaccine efficacy: 62·0% [56·6–66·7]), although efficacy against hospitalised dengue remained high (83·6% [76·8–88·4]).[16] To address the trend of waning efficacy observed during years 2 to 3, assessment of the effect of a booster dose approximately 4 years after the primary series was planned, with 25 months of follow-up.

After 3 years of follow-up, we aimed to evaluate the long-term efficacy and safety of TAK-003 up to 4·5 years after the primary series, as recommended by WHO;[17] vaccine performance against DENV-4, which had been limited by the small numbers of cases in previous analyses; and continued monitoring of DENV-3 cases for any evidence of higher risk of severe disease in dengue-naive TAK-003 recipients. TAK-003 has recently been approved for use in individuals with and without previous dengue infection in the EU, UK, and several dengue-endemic countries (Indonesia, Brazil, Argentina, and Thailand).[18,19] A positive scientific opinion was also received from the European Medicines Agency EU-M4all procedure, to facilitate access of the vaccine in low and middle-income countries.[20]

Here, we present the last 1·5 years of data from the 4·5-year follow-up period after the primary vaccination series, together with an evaluation of the cumulative data collected during the entire study before administration of a booster.

Methods

Study design and participants

This was a phase 3, double-blind, placebo-controlled, randomised trial with two parallel groups.[14–16,21] Healthy children and adolescents aged 4–16 years at the time of randomisation were eligible to participate and enrolled from April 26, 2016 (when the first participant signed an informed consent form) at 26 medical and research centres across eight countries (Brazil, Colombia, Dominican Republic, Nicaragua, Panama, Philippines, Sri Lanka, and Thailand), with the first injections being administered between Sept 7, 2016, and March 31, 2017. The main exclusion criteria were febrile illness (body temperature ≥38°C) at the time of randomisation, hypersensitivity or allergy to any of the vaccine components, pregnancy or breastfeeding, serious chronic or progressive disease, impaired or altered immune function, or previous receipt of a dengue vaccine. Full inclusion and exclusion criteria are listed in appendix 4 (pp 2–3). Demographics and medical history were captured on the electronic case report form. Sex was investigator-reported in the electronic case report form as a classification of male or female based on biological distinction using information from government-issued identification documents, where available. The study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Written informed assent or consent was obtained from all participants or their parents or legal guardians before enrolment. The protocol and informed consent forms were approved by the institutional review boards or local independent ethics committees (listed in appendix 4 p 1) before participant enrolment began.

Randomisation and masking

Participants were randomly assigned 2:1 to receive two doses of TAK-003 or placebo, administered subcutaneously 3 months apart (months 0 and 3). Randomisation was stratified by region (Asia or Latin America) and age (4–5, 6–11, or 12–16 years) using an interactive web response system and dynamic block assignment. A subgroup of 4000 randomly assigned participants was also randomly selected for additional safety and immunogenicity assessments (immunogenicity subset). Investigators, participants, parents and guardians, and sponsor representatives advising on trial conduct remained blinded to individual participant group randomisation throughout the study. Designated pharmacists or vaccine administrators were unmasked at each site and accessed randomisation information through a web portal but had no role in the collection or assessment of participant safety data. Medical writers and some sponsor-affiliated authors had access to both group and individual-level unblinded data, and other authors had access only to group-level unblinded data to prevent unblinding in this ongoing study. An independent data monitoring committee had access to unmasked data on request.

Procedures

The main phase of the study consisted of three parts for all participants. Part 1 was completed after participants had completed 12 months of follow-up after the second vaccination and at least 120 cases of virologically confirmed dengue had been reported. Part 2 continued for an additional 6 months, followed by a 3-year follow-up in part 3, evaluating long-term vaccine efficacy and safety. The protocol was amended to include a booster phase, with participants aged 4–11 years at study entry eligible to receive a booster dose after completing 4 years of follow-up from the second dose. Therefore, some

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See **Online** for appendix 4

participants did not complete the full 4·5 years of follow-up after the primary series, with the mean follow-up length in the last 6 months of the study being 169·6 days (SD 30·63) in booster recipients at database lock (n=7276) and 186·3 days (20·94) in non-recipients (n=10 348). The booster phase is ongoing at the time of writing this Article, with a follow-up of 25 months planned in parts 4 and 5 of the study. This Article reports the findings to the end of part 3 of the study.

Participants (or their parents or guardians) were contacted at least weekly to monitor for febrile illnesses and aid in robust identification of symptomatic dengue cases (see appendix 4 p 4). Cases were virologically confirmed by serotype-specific RT-PCR (PPD Laboratories, Richmond, VA, USA) using a protocol adapted from Santiago and colleagues,[22] with case management performed according to local practice. The severity of virologically confirmed dengue was assessed by a blinded independent Dengue Case Severity Adjudication Committee (DCAC)[14,21] and using programmed WHO 1997 dengue haemorrhagic fever criteria[23] (appendix 4 pp 3–4).

Both TAK-003 (0·5 mL dose) and placebo (0·5 mL dose) were administered subcutaneously into the upper arm (appendix 4 p 4).

Blood samples were taken at baseline and month 4 (1 month after the second dose) from all participants for the assessment of dengue serotype-specific neutralising antibodies by microneutralisation assay. Baseline seropositivity was defined as a microneutralisation titre of 10 or greater against at least one DENV serotype; participants with microneutralisation titres of less than 10 against all four serotypes at baseline were considered seronegative. Additional blood samples were taken at months 1, 3, 9, and 15, and annually from participants in the immunogenicity subset. Data on serious adverse events and adverse events leading to discontinuation were collected for all participants throughout the study. Details of other safety evaluations performed in part 1 of the study (solicited and unsolicited adverse events) have been published previously,[14] as have safety findings up to the end of year 3.[15,16,21]

Outcomes

The cumulative vaccine efficacy of two doses of TAK-003 in preventing virologically confirmed dengue and hospitalised virologically confirmed dengue from first dose to the end of part 3 (approximately 57 months) was analysed (exploratory endpoints). Prevention of dengue haemorrhagic fever, severe dengue, and dengue haemorrhagic fever or severe dengue after TAK-003 vaccination was also analysed. Vaccine efficacy in preventing virologically confirmed dengue and hospitalised virologically confirmed dengue during year 4 (months 40 to 51 after the first dose) and during the last 18 months of part 3 (months 40 to 57 after the first dose) is reported for the per protocol analysis set (ie, all participants with no major protocol violations; see appendix 4 p 4 for further details) as part of the exploratory outcomes. Clinical signs and symptoms of virologically confirmed dengue cases from first dose to the end of part 3 by baseline serostatus are reported for the safety set (ie, all randomly assigned participants who received at least one dose of TAK-003 or placebo). Safety set data (deaths, related serious adverse events, and serious adverse events deemed relevant in the context of vaccine safety by the investigator) are presented for part 3 of the trial (approximately 22–57 months after the first dose). Serious adverse events were coded according to the Medical Dictionary for Regulatory Activities (version 21.0). Immunogenicity is evaluated across parts 1 to 3 of the study as follows: geometric mean titres of neutralising antibodies are presented for each DENV serotype at month 0 (pre-vaccination), month 1, 3, 4, 9, and 15, and then annually up to 51 months after the first dose (per protocol set for immunogenicity). Seropositivity rates for each DENV serotype at 51 months after the first dose are also presented (per protocol set for immunogenicity). For practical considerations and to capture real-life scenarios, case management followed local practices and resulted in heterogeneity in hospitalisation rates in the participating countries. Given the substantially higher rate of dengue case hospitalisations in Sri Lanka compared with other countries observed throughout the trial (see Rivera and colleagues for discussion and further details[16]), additional exploratory analyses excluding Sri Lankan data are presented.

Statistical analysis

Full details of sample size calculations have been published previously;[14] see appendix 4 p 4 for details. Vaccine efficacy was assessed on the per protocol set. Cumulative vaccine efficacy since the first dose was assessed for the safety set. Vaccine efficacy was defined as $1–(\lambda V/\lambda C)$, where λV and λC denote the hazard rates for the TAK-003 and placebo groups, respectively, and was expressed as a percentage. Efficacy endpoints were analysed as follows: hazard ratios (HR) and corresponding 95% CIs were estimated using a Cox proportional-hazards model with treatment group as a factor, adjusted for age and stratified by region; the region stratification was prospectively chosen in case the proportional-hazard assumption was not consistent across the two regions. Safety data are summarised and presented for the safety set. Immunogenicity analyses were performed for the per protocol set for immunogenicity (ie, all randomised participants in the subset for whom a valid pre-dosing and at least one valid post-dosing blood sample was received for immunogenicity analysis, and who had no major protocol violations). Immunogenicity endpoints are summarised using descriptive statistics and 95% CIs by group and for each visit. All analyses were performed using SAS (version 9.4).

This study is registered with ClinicalTrials.gov, NCT02747927.

Role of the funding source

Takeda was responsible for the overall study design (taking into consideration investigators' input), study site selection, and performing data analysis. The investigators were responsible for study participant enrolment and management, data collection, as well as day-to-day study site operations. Takeda employees and subcontractors had a role in designing the study; data collection, analyses, and interpretation; and in the writing and critical review of this report.

Results

Of 23 401 participants who were screened for eligibility, 20 099 participants were randomly assigned to receive either TAK-003 (n=13 401) or placebo (n=6698) with the first dose administered between Sept 7, 2016, and March 31, 2017. Enrolment was broadly balanced between Asia (8991 [44·8%] of 20 071 participants) and Latin America (11 080 [55·2%] of 20 071 participants; safety set). Participant demographics and baseline clinical characteristics are summarised in table 1. Participants had a mean age of 9·6 (SD 3·35) years and 5547 (27·6%) of 20 063) had no previous exposure to DENV at baseline (safety set).

Of the 20 071 participants who received first vaccination, 18 257 (91·0%) completed part 3 of the trial (figure 1). During the approximately 57 months after the first dose, 9698 (in the placebo group) and 17 978 (in the TAK-003 group) febrile illnesses were reported. Virologically confirmed dengue was detected in 560 (5·8%) of the 9698 febrile illnesses reported in the placebo group and 447 (2·5%) of the 17 978 febrile illnesses reported in the TAK-003 group, of which 142 (25%) of 560 and 46 (10%) of 447 were hospitalised (appendix 4 p 5). Proportionally fewer cases of virologically confirmed dengue were detected during the last 18 months (placebo: 57 of 560; TAK-003: 55 of 447), with hospitalisation rates similar to those observed in the study as a whole (placebo: 16 [28%] of 57 *vs* 142 [25%] of 560; TAK-003: four [7%] of 55 *vs* 46 [10%] of 447; appendix 4 p 5). All four serotypes were detected in Asia, whereas most virologically confirmed dengue cases in Latin America were caused by DENV-1 and DENV-2 (appendix 4 p 15).

The cumulative vaccine efficacy of TAK-003 was 61·2% (95% CI 56·0–65·8) against virologically confirmed dengue and 84·1% (77·8–88·6) against hospitalised virologically confirmed dengue from the first dose to approximately 4·5 years after the second dose (safety set; figure 2). TAK-003 was efficacious against virologically confirmed dengue caused by all four serotypes in baseline seropositive participants, with efficacy estimates ranging from 52·3% (36·7–64·0) against DENV-3 to 80·4% (73·1–85·7) against DENV-2 (figure 2A). In baseline seronegative participants,

	Safety set		Per protocol set	
	Placebo (n=6687)	TAK-003 (n=13 380)	Placebo (n=6317)	TAK-003 (n=12 704)
Age, mean (SD), years	9·6 (3·34)	9·6 (3·36)	9·6 (3·34)	9·6 (3·35)
Age group				
4–5 years	846 (12·7%)	1702 (12·7%)	801 (12·7%)	1620 (12·8%)
6–11 years	3697 (55·3%)	7387 (55·2%)	3492 (55·3%)	7010 (55·2%)
12–16 years	2144 (32·1%)	4291 (32·1%)	2024 (32·0%)	4074 (32·1%)
Sex				
Male	3411 (51·0%)	6729 (50·3%)	3219 (51·0%)	6390 (50·3%)
Female	3276 (49·0%)	6651 (49·7%)	3098 (49·0%)	6314 (49·7%)
Race*				
American Indian or Alaska Native	2621 (39·2%)	5234 (39·1%)	2378 (37·6%)	4819 (37·9%)
Asian	2985 (44·6%)	5988 (44·8%)	2934 (46·4%)	5888 (46·3%)
Black or African American	758 (11·3%)	1451 (10·8%)	706 (11·2%)	1351 (10·6%)
Native Hawaiian or other Pacific Islander	1 (<0·1%)	2 (<0·1%)	1 (<0·1%)	2 (<0·1%)
White	149 (2·2%)	329 (2·5%)	131 (2·1%)	284 (2·2%)
Multiracial	170 (2·5%)	376 (2·8%)	165 (2·6%)	360 (2·8%)
Region				
Asia	2993 (44·8%)	5996 (44·8%)	2942 (46·6%)	5896 (46·4%)
Latin America	3694 (55·2%)	7384 (55·2%)	3375 (53·4%)	6808 (53·6%)
Baseline serostatus, n/N (%)				
Seropositive	4854/6684 (72·6%)	9663/13 375 (72·2%)	4588/6314 (72·7%)	9167/12 700 (72·2%)
Seronegative	1832/6684 (27·4%)	3714/13 375 (27·8%)	1726/6314 (27·3%)	3533/12 700 (27·8%)

Data are n (%) unless otherwise stated. *Data missing for three participants (<0·1%) in the placebo group (safety set data) and two participants (<0·1%) in the placebo group (per protocol set data). For baseline serostatus, percentages are based on the number of participants/number of evaluable participants. Baseline seropositivity is defined as a reciprocal neutralising titre of 10 or more for at least one dengue virus serotype.

Table 1: **Baseline characteristics**

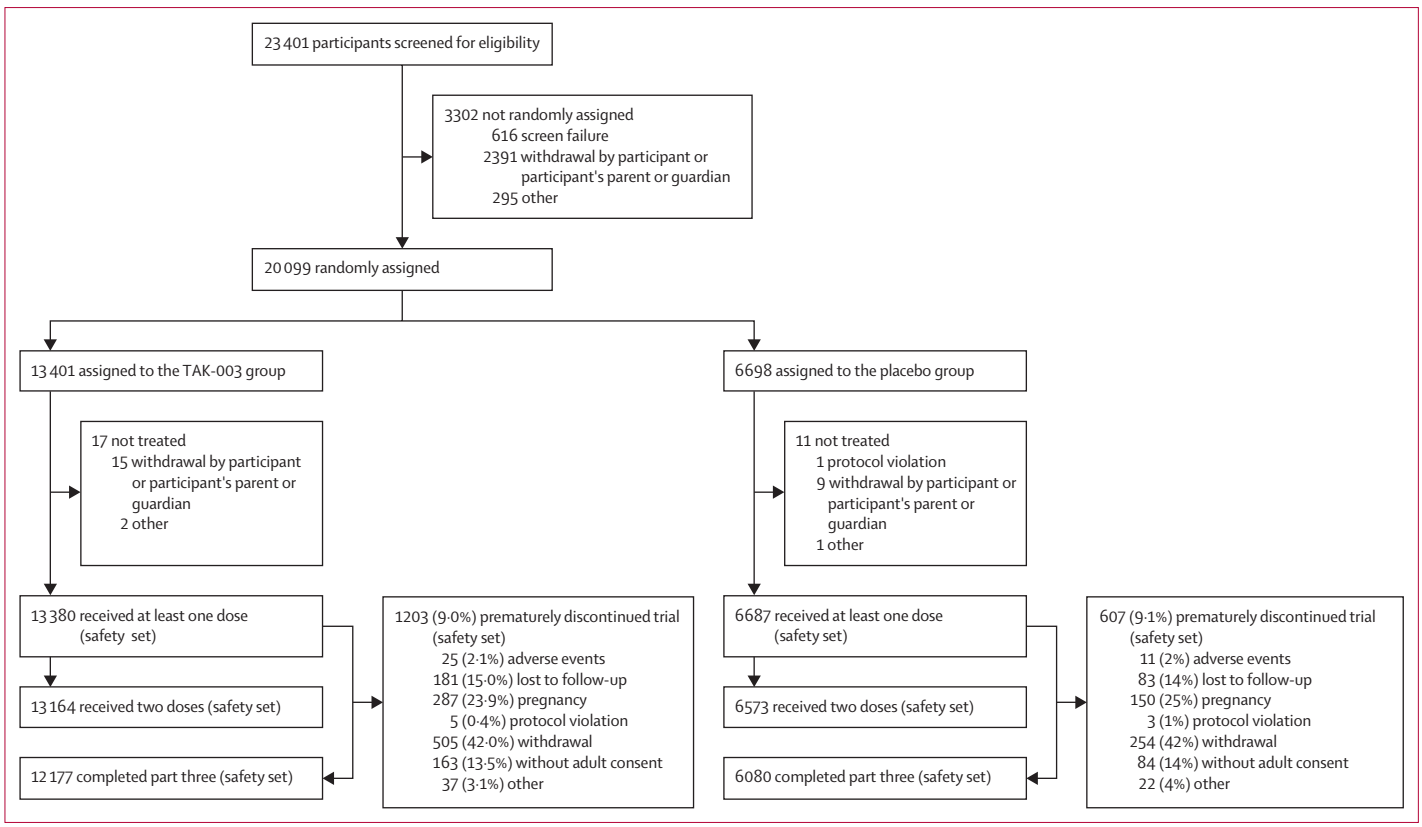

Figure 1: **Trial profile**
Four participants received both TAK-003 and placebo because of an administrative error; these participants are not shown under the TAK-003 or placebo groups.

TAK-003 had efficacy of 45·4% (26·1–59·7) against DENV-1 and 88·1% (78·6–93·3) against DENV-2; no efficacy was observed against DENV-3 (–15·5 [–108·2 to 35·9]), and the number of virologically confirmed dengue cases of DENV-4 remained very low but did not indicate efficacy (–105·6 [–628·7 to 42·0]; figure 2A). Overall, the cumulative incidence of virologically confirmed dengue in the approximately 57 month follow-up period was higher in the placebo group than the TAK-003 group, irrespective of baseline serostatus (safety set; figure 3A; appendix 4 p 16).

Efficacy data on hospitalised virologically confirmed dengue are reported along with a sensitivity analysis excluding data from Sri Lanka. Throughout the study, hospitalised virologically confirmed dengue rates were higher in Sri Lanka than in other participating countries (70 [68%] of 103 in the placebo group of Sri Lanka *vs* 72 [16%] of 457 in the placebo group of the other seven participating countries; safety set; appendix 4 p 6), as cases were proactively hospitalised for close monitoring according to local practice. Cumulative vaccine efficacy against hospitalised virologically confirmed dengue remained high at 85·9% (95% CI 78·7–90·7) in baseline seropositive participants and was observed against all serotypes, ranging from 66·8% (37·4–82·3) against DENV-1 to 100% (95% CI non-estimable) against DENV-4 (figure 2B), although the latter involved a small number of cases (n=3; figure 2B). The exclusion of Sri Lankan data resulted in similar vaccine efficacy estimates (figure 2B). Vaccine efficacy against dengue haemorrhagic fever and DCAC-defined severe dengue among baseline seropositive participants was high, irrespective of data from Sri Lanka, with estimates ranging from 78·7% (17·5–94·5) to 90·2% (16·4–98·9).

In baseline seronegative participants (corresponding to 5547 [27·6%] of 20 063 participants in the safety set population), cumulative vaccine efficacy against hospitalised virologically confirmed dengue was high at 79·3% (95% CI 63·5–88·2) overall and was observed against DENV-1 (78·4% [43·9–91·7]) and DENV-2 (100% [non-estimable]; 23 cases, all in the placebo group). Only 14 participants with DENV-3 (placebo group, n=3; TAK-003 group, n=11) and one participant with DENV-4 (in the placebo group) were hospitalised, precluding robust estimates. In the TAK-003 group, although all six DENV-3 cases in Sri Lanka were hospitalised (all reported from a single trial site), only five of the remaining 30 DENV-3 cases outside Sri Lanka were hospitalised. The exclusion of data from Sri Lanka removed the imbalance (hospitalisation of a higher proportion of TAK-003 recipients *vs* placebo recipients) observed for DENV-3

without impacting the efficacy observed for other serotypes. The sparse data on dengue haemorrhagic fever and DCAC-defined severe cases in seronegative participants were largely dominated by DENV-3 and did not suggest efficacy, although the exclusion of data from Sri Lanka changed vaccine efficacy (95% CI) against

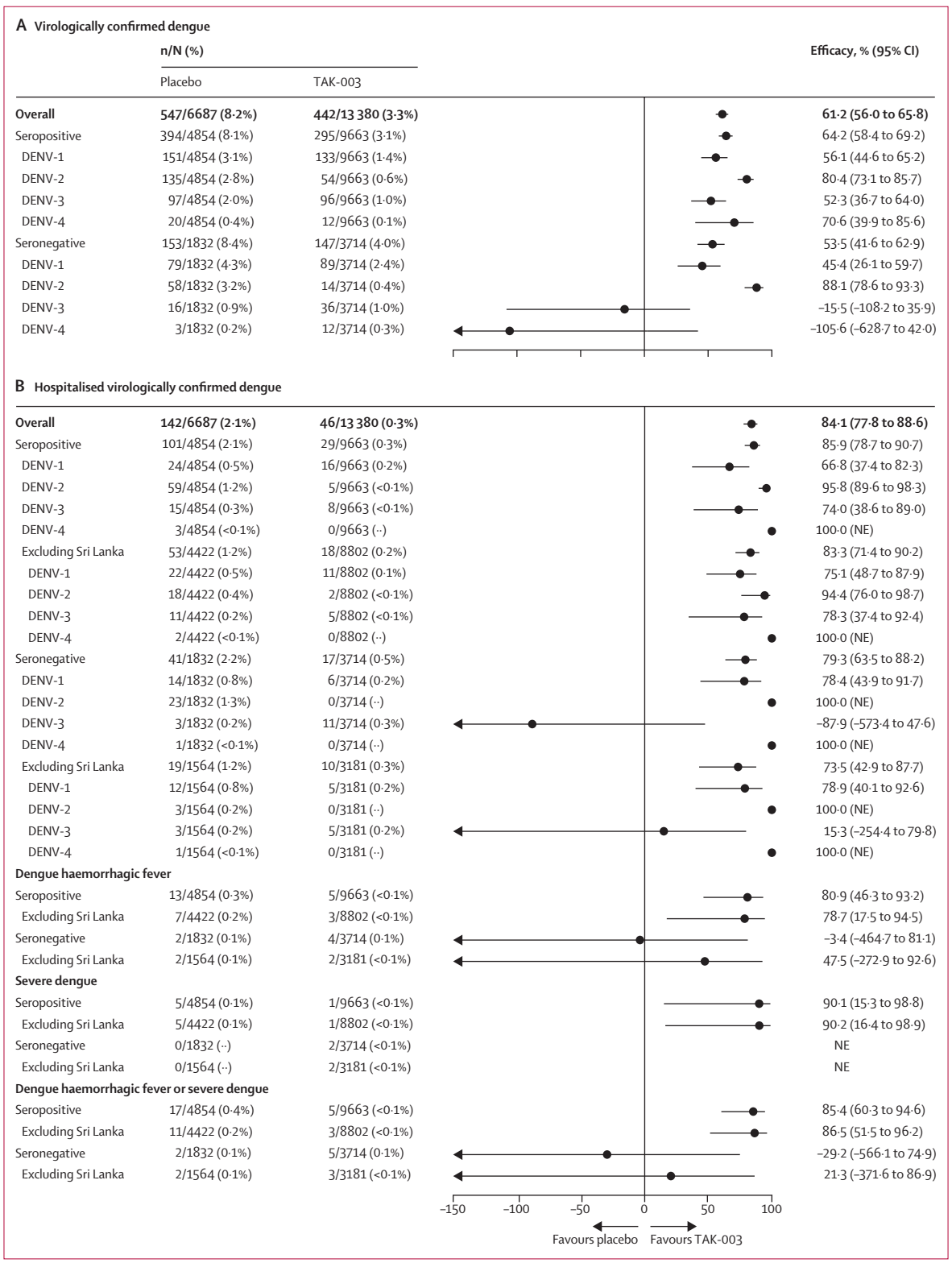

Figure 2: **Efficacy of TAK-003 in preventing virologically confirmed dengue (A) and hospitalised virologically confirmed dengue, dengue haemorrhagic fever, and DCAC-defined severe dengue (B)**
Data are for the safety set and are presented from the first dose to up to 4·5 years after the second dose (approximately month 57 after the first dose) by baseline serostatus. Dengue haemorrhagic fever by serostatus (across groups): 18 seropositive (DENV-1: n=5; DENV-2: n=7; DENV-3: n=5; and DENV-4: n=1) and six seronegative (DENV-1: n=1; and DENV-3: n=5). Severe dengue by serostatus (across groups): six seropositive (DENV-1: n=1; DENV-2: n=1; DENV-3: n=4) and two seronegative (DENV-3: n=2). Cases meeting both definitions (across groups): two seropositive (both DENV-3) and one seronegative (DENV-3). DCAC=Dengue Case Severity Adjudication Committee. DENV=dengue virus. NE=non-estimable.

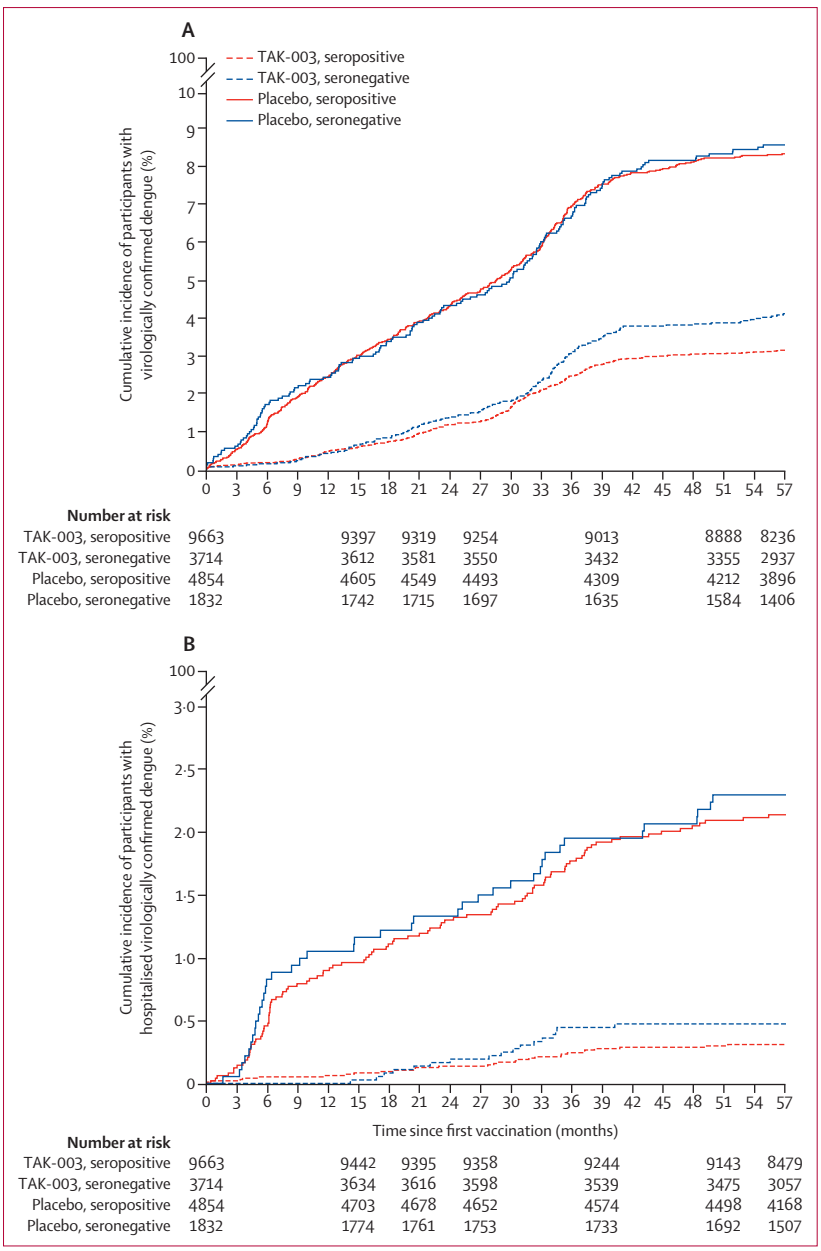

Figure 3: **Cumulative incidence of virologically confirmed dengue (A) and hospitalised virologically confirmed dengue (B)**

Data are for the safety set and are presented from the first dose to up to 4·5 years after the second dose (approximately month 57 after the first dose) and are truncated at month 57.

dengue haemorrhagic fever from –3·4 (–646·7 to 81·1) to 47·5 (–272·9 to 92·6).

The cumulative incidence of hospitalised virologically confirmed dengue over the approximately 57-month follow-up period was higher in the placebo group compared with the TAK-003 group, irrespective of serostatus (safety set; figure 3B).

Vaccine efficacy against virologically confirmed dengue was 62·8% (95% CI 41·4–76·4) during year 4; efficacy was 64·1% (37·4–79·4) in baseline seropositive participants and 60·2% (11·1–82·1) in baseline seronegative participants (per protocol set; table 2). For hospitalised virologically confirmed dengue, vaccine efficacy was 96·4% (72·2–99·5) during year 4, with similarly high vaccine efficacy, irrespective of baseline serostatus (94·0% [52·2–99·3] in seropositive participants, and 100% [non-estimable] in seronegative participants). Although case counts were small at the serotype level, distributions were generally in line with the cumulative serotype-level efficacy data. Appendix 4 (pp 7–8) includes a year-by-year analysis at serotype level (per protocol set). The data for the last 18 months were generally in line with the year 4 data.

There was evidence of a favourable effect of TAK-003 on clinical manifestation and severity of disease in participants with virologically confirmed dengue, compared with placebo. Clearer trends were observed in seropositive participants (safety set; appendix 4 p 9) than seronegative participants (safety set; appendix 4 p 10), and the exclusion of data from Sri Lanka did not change the overall interpretation. Levels of viremia (point estimates) were numerically similar or lower in the TAK-003 versus the placebo group (safety set; appendix p 11).[16] Interpretation was limited by the small case numbers for some of the comparisons, particularly for hospitalised virologically confirmed dengue, together with variability in the interval between fever onset and sampling for RT-PCR.

Rates of serious adverse events during part 3 of the study were similar in the placebo and TAK-003 groups, irrespective of baseline serostatus (seropositive participants who reported one or more serious adverse events: 291 [6·0%] of 4854 participants in the placebo group and 481 [5·0%] of 9663 participants in the TAK-003 group; seronegative participants who reported one or more serious adverse events: 105 [5·7%] of 1832 and 183 [4·9%] of 3714; safety set; table 3). No serious adverse events were considered related to the investigational product or study procedures for either group. Serious adverse events (by system organ class and severity) by baseline serostatus are listed in appendix 4 (pp 12–14). For infections and infestations, dengue fever and dengue haemorrhagic fever were reported for: 61 (1·3%; dengue fever) and ten (0·2%; dengue haemorrhagic fever) of 4854 placebo recipients, and 38 (0·4%) and three (<0·1%) of 9663 TAK-003 recipients (baseline seropositive participants); and 22 (1·2%) and two (0·1%) of 1832 placebo recipients, and 18 (0·5%) and six (0·2%) of 3714 TAK-003 recipients (baseline seronegative participants). In proportion to the placebo:TAK-003 randomisation ratio of 1:2, six deaths occurred in the placebo group (traumatic lung injury, adenocarcinoma of colon, disseminated intravascular coagulation, drowning, suicide, and road traffic accident) and 11 in the TAK-003 group (wounds [n=2], road traffic accident, head injury, suicide [n=3], multiple organ dysfunction syndrome, gastrointestinal haemorrhage, craniocerebral injury, and asphyxia). None of the deaths were considered related to the study vaccine.

	Placebo		TAK-003		Efficacy, % (95% CI)
	n/N (%)	Person-years at risk	n/N (%)	Person-years at risk	
Year 4 (month 40–51)					
Virologically confirmed dengue					
Overall	42/6103 (0·7%)	5534·4	33/12 225 (0·3%)	11 709·6	62·8 (41·4 to 76·4)
Seropositive	29/4425 (0·7%)	4014·3	22/8820 (0·2%)	8471·1	64·1 (37·4 to 79·4)
Seronegative	13/1677 (0·8%)	1519·1	11/3403 (0·3%)	3236·5	60·2 (11·1 to 82·1)
Seropositive					
DENV-1	18/4425 (0·4%)	4019·4	16/8820 (0·2%)	8475·6	57·7 (17·0 to 78·4)
DENV-2	6/4425 (0·1%)	4029·1	4/8820 (<0·1%)	8483·8	68·3 (−12·5 to 91·1)
DENV-3	2/4425 (<0·1%)	4030·8	2/8820 (<0·1%)	8484·6	52·4 (−238·2 to 93·3)
DENV-4	3/4425 (<0·1%)	4031·1	0/8820	8486·4	100·00 (NE)
Seronegative					
DENV-1	11/1677 (0·7%)	1519·5	10/3403 (0·3%)	3236·8	57·1 (−0·9 to 81·8)
DENV-2	1/1677 (<0·1%)	1527·7	0/3403	3244·5	100·00 (NE)
DENV-3	1/1677 (<0·1%)	1527·5	0/3403	3244·5	100·00 (NE)
DENV-4	0/1677	1527·8	1/3403 (<0·1%)	3244·2	NE
Hospitalised virologically confirmed dengue					
Overall	13/6103 (0·2%)	5554·5	1/12 225 (<0·1%)	11 732·7	96·4 (72·2 to 99·5)
Seropositive	8/4425 (0·2%)	4027·8	1/8820 (<0·1%)	8486·2	94·0 (52·2 to 99·3)
Seronegative	5/1677 (0·3%)	1525·7	0/3403	3244·5	100·0 (NE)
Seropositive					
DENV-1	3/4425 (<0·1%)	4029·6	1/8820 (<0·1%)	8486·2	84·2 (−51·9 to 98·4)
DENV-2	4/4425 (<0·1%)	4030·5	0/8820	8486·4	100·0 (NE)
DENV-3	1/4425 (<0·1%)	4031·8	0/8820	8486·4	100·0 (NE)
DENV-4	0/4425	4032·1	0/8820	8486·4	NE
Seronegative					
DENV-1	3/1677 (0·2%)	1526·2	0/3403	3244·5	100·0 (NE)
DENV-2	1/1677 (<0·1%)	1527·7	0/3403	3244·5	100·0 (NE)
DENV-3	1/1677 (<0·1%)	1527·5	0/3403	3244·5	100·0 (NE)
DENV-4	0/1677	1527·8	0/3403	3244·5	NE
Last 18 months (month 40 to 57)					
Virologically confirmed dengue					
Overall	52/6102 (0·9%)	8211·0	49/12 224 (0·4%)	17 404·7	55·7 (34·5 to 70·0)
Seropositive	35/4425 (0·8%)	5968·3	30/8820 (0·3%)	12 617·0	59·6 (34·2 to 75·2)
Seronegative	17/1676 (1·0%)	2241·2	19/3402 (0·6%)	4784·7	46·9 (−2·1 to 72·4)
Seropositive					
DENV-1	20/4425 (0·5%)	5979·8	17/8820 (0·2%)	12 625·8	59·6 (22·8 to 78·8)
DENV-2	9/4425 (0·2%)	5996·4	11/8820 (0·1%)	12 639·0	42·6 (−38·7 to 76·2)
DENV-3	2/4425 (<0·1%)	6000·6	2/8820 (<0·1%)	12 642·1	52·4 (−238·3 to 93·3)
DENV-4	4/4425 (<0·1%)	6000·0	0/8820	12 645·0	100·0 (NE)
Seronegative					
DENV-1	13/1676 (0·8%)	2243·1	11/3402 (0·3%)	4787·0	60·2 (11·1 to 82·2)
DENV-2	3/1676 (0·2%)	2256·5	4/3402 (0·1%)	4799·1	35·7 (−187·3 to 85·6)
DENV-3	1/1676 (<0·1%)	2256·8	0/3402	4799·9	100·0 (NE)
DENV-4	0/1676	2257·6	4/3402 (0·1%)	4798·5	NE

(Table 2 continues on next page)

Geometric mean titres of neutralising antibodies remained higher in the TAK-003 group than in the placebo group through month 51 for each of the serotypes, irrespective of baseline serostatus (per protocol set for immunogenicity data; appendix 4 p 17). In baseline seronegative participants, a pattern of gradual rise in antibody titres was observed over time in the placebo group, presumably related to natural dengue exposure, and seropositivity rates (titre ≥10) at month 51 of 21% [n=59/287] to 24% [70/287] against individual

	Placebo		TAK-003		Efficacy, % (95% CI)
	n/N (%)	Person-years at risk	n/N (%)	Person-years at risk	
(Continued from previous page)					
Hospitalised virologically confirmed dengue					
Overall	15/6102 (0·2%)	8428·9	2/12 224 (<0·1%)	17 446·8	93·7 (72·4 to 98·6)
Seropositive	10/4425 (0·2%)	5994·3	2/8820 (<0·1%)	12 643·9	90·4 (56·4 to 97·9)
Seronegative	5/1676 (0·3%)	2253·1	0/3402	4799·9	100·0 (NE)
Seropositive					
DENV-1	3/4425 (<0·1%)	5998·9	2/8820 (<0·1%)	12 643·9	68·2 (−90·2 to 94·7)
DENV-2	6/4425 (0·1%)	5999·1	0/8820	12 645·0	100·0 (NE)
DENV-3	1/4425 (<0·1%)	6002·1	0/8820	12 645·0	100·0 (NE)
DENV-4	0/4425	6002·9	0/8820	12 645·0	NE
Seronegative					
DENV-1	3/1676 (0·2%)	2254·5	0/3402	4799·9	100·0 (NE)
DENV-2	1/1676 (<0·1%)	2257·0	0/3402	4799·9	100·0 (NE)
DENV-3	1/1676 (<0·1%)	2256·8	0/3402	4799·9	100·0 (NE)
DENV-4	0/1676	2257·6	0/3402	4799·9	NE

Data are for year 4 (month 40–51 after the first dose) and the last 18 months (month 40–57 after first dose) in the per protocol set. The reference point for the yearly intervals is the date of second vaccination, whereas the reference point for the last-18-months interval is the end of part 2. Some participants had a duration of follow-up in part 2 of more than 6 months. The start of year 4 and the last 18 months does not overlap for all participants. Person-years at risk is defined as cumulative time in years until the start of virologically confirmed dengue fever or until the end of the respective study part or discontinuation date, whichever comes first. DENV=dengue virus. NE=non-estimable.

Table 2: **Vaccine efficacy of TAK-003 in preventing virologically confirmed dengue and hospitalised virologically confirmed dengue during year 4 and the last 18 months of part 3**

serotypes (per protocol set for immunogenicity data). In comparison, seropositivity rates were between 84% (465/554) and 100% (552/554) at month 51 in the TAK-003 group.

Discussion

This analysis demonstrates the long-term efficacy of TAK-003 administered 3 months apart in baseline seronegative and seropositive participants. Vaccine efficacy against virologically confirmed dengue up to 4·5 years after receipt of the primary vaccination series was 53·5% (95% CI 41·6–62·9) in baseline seronegative participants and 64·2% (58·4–69·2) in baseline seropositive participants. Vaccine performance remained higher against hospitalised virologically confirmed dengue cases than against symptomatic virologically confirmed dengue cases throughout the follow-up period, with efficacy of 79·3% (63·5 to 88·2) in seronegative participants and 85·9% (78·7 to 90·7) in seropositive participants. Although an imbalance in cases of DENV-3 hospitalised virologically confirmed dengue was observed (ie, numerically higher cases in the TAK-003 group *vs* the placebo group after accounting for the 2:1 randomisation ratio), it largely reflects the higher rate of hospitalisation at the Sri Lankan trial sites. Therefore, it is assumed to be a chance observation in the context of multi-level subgroup analysis (see Rivera and colleagues for details[16]). Per 100 000 vaccinated participants, these efficacy data and the observed background dengue incidence extrapolate to a reduction of 4393 virologically confirmed dengue cases (1780 hospitalised virologically confirmed dengue) in seronegative participants and 5064 virologically confirmed dengue cases (1780 hospitalised virologically confirmed dengue) in seropositive participants, representing considerable population-level impact in a setting similar to that evaluated in this study. Of note, the transmission dynamics of DENV serotypes are complex and remain largely unpredictable.[24]

The data presented in this report demonstrate an overall favourable profile in both dengue-naive participants and previously exposed participants. Although the efficacy profile varied by serotype, it remains challenging not only to develop a dengue vaccine that has uniform efficacy across serotypes but also to generate robust serotype-level data in a pre-licensure setting. Assessing vaccine efficacy against virologically confirmed dengue and hospitalised virologically confirmed dengue for all four DENV serotypes can be difficult owing to the erratic and unpredictable nature of dengue epidemiology; however, we were able to collect data for all four serotypes in this trial, albeit limited in some subgroups (eg, DENV-4 in baseline seronegative participants).

This follow-up aimed to assess the long-term impact of vaccination beyond the short-term cross-protection believed to be induced by a DENV infection and possibly also by vaccination. Results from year 4 demonstrate that the protection provided by TAK-003 is not short-term cross-protection. This conclusion is strengthened by the

efficacy during year 4 being mainly attributable to DENV-1, not to the non-chimeric (backbone) TDV-2 component of the vaccine. Although no consensus exists about the precise duration of cross-protection, the 4·5-year follow-up duration of this trial is much longer than the typical duration of cross-protection reported in the literature (ie, a few months to a couple of years)[25,26] or the inflection point of increased risk of hospitalised dengue in seronegative participants in CYD-TDV trials (ie, approximately 1 year after the third dose).[10]

Previously, we have reported fluctuation in vaccine efficacy estimates between year 2 and year 3 in baseline seronegative participants in the 4–5 years age group (–23·7% [95% CI –219·1 to 52·0] in year 2 *vs* 47·4% [–4·3 to 73·4] in year 3).[16] Similar trends were observed in the estimation of vaccine efficacy against DENV-1 in seronegative participants (17·2% [–31·8 to 47·9] in year 3 *vs* 57·1% [–0·9 to 81·8] in year 4) and DENV-2 in seropositive participants (68·3% [–12·5 to 91·1] during year 4 *vs* 42·6% [–38·7 to 76·2] in the last 18 months that included year 4). These observations are biologically implausible and highlight the inherent variability in multi-level subgroup analysis and the risk of over-interpretation or misinterpretation.

The overall efficacy against virologically confirmed dengue was 62·8% (95% CI 41·4–76·4) in year 4 versus 55·7% (34·5–70·0) during the last 18 months including year 4. The corresponding efficacy against hospitalised virologically confirmed dengue was 96·4% (72·2–99·5) and 93·7% (72·4–98·6), respectively. The numerical differences need cautious interpretation in view of above-described fluctuations in estimates in yearly intervals. Additionally, not all participants completed the last 6 months of the 4·5 year follow-up period due to enrolment in the booster phase after year 4, or would have passed through the peak of the dengue season in their areas.

In a previous analysis of data by age group, a lower efficacy against virologically confirmed dengue (from first dose to 3 years after the second dose) in 4–5-year-old participants was observed compared with older participants, although a detailed analysis did not indicate a clear age effect (vaccine efficacy [95% CI]: 42·3% [22·5–57·0] in 4–5-year-olds; 64·6% [57·8–70·4] in 6–11-year olds; 68·9% [58·7–76·6] in 12–16-year-olds).[16] The corresponding efficacy against hospitalised virologically confirmed dengue were 50·6% (–13·9 to 78·6), 85·7% (77·3–91·0), and 89·1% (76·6–94·9), respectively.[16] The additional data in the last 18 months did not change this overall trend. A detailed analysis will be reported separately.

Since our report of primary endpoints in 2019,[14] which suggested potential differences in efficacy by serotype, we have evaluated the data similarly in each of our subsequent reports.[15,16,21] This has resulted in eight sets of analysis each for virologically confirmed dengue and hospitalised virologically confirmed dengue, which is especially difficult to evaluate in the seronegative population, which comprised just 28% of the 4–16-year-old study cohort. DENV-1 and DENV-2 were detected most frequently in the study across the eight Asian and Latin American countries. DENV-3 and DENV-4 were observed less frequently and were mostly reported from the three Asian countries. Although all four serotypes frequently co-circulate, and serotype dominance fluctuates over time, the serotype distribution in the study represented a scenario consistent with decades of epidemiological trends.[24]

Previously, we reported that the data revealed a lack of efficacy against DENV-3 in the seronegative population, and efficacy against DENV-4 in that subpopulation could not meaningfully be assessed owing to low incidences in the early phase of the study when the vaccine is supposed to be fully effective.[16,21] Likewise, the small number of DENV-3 cases (n=1) and DENV-4 cases (n=5, including 1 second episode of virologically confirmed dengue) during the last 18 months precluded a conclusive assessment in that subpopulation. Importantly, the vaccine safety profile remained favourable during that

	Placebo (n=6687)	TAK-003 (n=13 380)
Person-years of follow-up	19 193·9	38 366·9
Seropositive		
Participants	4854 (72·6%)	9663 (72·2%)
Person-years of follow-up	13 943·2	27 761·9
Any	291 (6·0%)	481 (5·0%)
Mild	29 (0·6%)	69 (0·7%)
Moderate	225 (4·6%)	357 (3·7%)
Severe	37 (0·8%)	55 (0·6%)
Related to investigational product*	0	0
Related to study procedures	0	0
Leading to study discontinuation	5 (0·1%)	9 (<0·1%)
Deaths	5 (0·1%)	9 (<0·1%)
Seronegative		
Participants	1832 (27·4%)	3714 (27·8%)
Person-years of follow-up	5247·7	10 596·0
Any	105 (5·7%)	183 (4·9%)
Mild	13 (0·7%)	33 (0·9%)
Moderate	75 (4·1%)	131 (3·5%)
Severe	17 (0·9%)	19 (0·5%)
Related to investigational product*	0	0
Related to study procedures	0	0
Leading to study discontinuation	1 (<0·1%)	2 (<0·1%)
Deaths	1 (<0·1%)	2 (<0·1%)

Data are n (%) unless otherwise stated. Data reported for the safety set during part 3 of the trial (approximately months 22 to 57 after the first dose).
*Relationship to trial vaccine as assessed by the investigator.

Table 3: **Participants experiencing serious adverse events during part 3 of the trial by baseline serostatus**

time, with no reported breakthrough cases of DENV-3 and DENV-4 that led to hospitalisation or were dengue haemorrhagic fever or DCAC-defined severe dengue for the few cases reported during that time.

The study revealed efficacy against dengue haemorrhagic fever or DCAC-defined severe dengue in the seropositive population, irrespective of Sri Lankan data. However, the data for the seronegative population remained sparse and were dominated by DENV-3 cases. In interpreting these data, we considered the following: first, the overall extremely small number of severe dengue cases; second, serotype-specific epidemiology, which suggests that DENV-3 from southeast Asia displays the highest proportion of severe cases in primary infections;[27] third, the lack of efficacy against DENV-3, combined with the higher likelihood of detecting rare events in the TAK-003 group owing to the 2:1 randomisation; fourth, the potential confounding effect of Sri Lankan data (ie, local clinical practice standard that led to a greater rate of dengue haemorrhagic fever detection as evident in the placebo group [appendix 4 p 6]); and fifth, an increase in disease severity was not observed in the study population during long-term follow-up.

The data from overall virologically confirmed dengue cases in the study (560 in the placebo group and 447 in the TAK-003 group; 1:2 randomisation) suggest a favourable impact of vaccination on the manifestation of breakthrough cases. We hypothesise that TAK-003, which has a DENV backbone and elicits a broad spectrum of humoral and cellular immune responses (eg, functional anti-NS1 cross-reactive antibodies and a DENV-specific polyfunctional cell-mediated immune response),[28,29] has a disease-modifying effect. It likely also explains the high level of efficacy against hospitalised virologically confirmed dengue.

In accordance with the findings of the largest phase 2 trial with TAK-003, levels of neutralising antibody titres remained elevated 4 years after the last dose compared with placebo.[30] In light of the year 4 efficacy data, it is plausible to assume benefit beyond the 4·5-year follow-up period. It is believed that a repeat dengue infection with a different serotype induces a qualitatively and quantitatively distinct immune response profile with a broad cross-neutralising capacity. In human cohort studies, this phenomenon is regarded as the most likely explanation for mild to inapparent manifestation of tertiary infections.[31] We believe that individuals exposed to natural dengue infections following immunisation with TAK-003 might transition to a post-secondary-like state and obtain an indirect benefit. This includes seronegative participants who may not get direct protection against primary infection with DENV-3.

Data from these exploratory analyses are broadly consistent with the results reported previously in that TAK-003 provides protection against symptomatic dengue and dengue leading to hospitalisation. High vaccine efficacy against virologically confirmed dengue leading to hospitalisation and variable efficacy trends according to serotype has been consistently observed across the reported analyses.[14–16] Importantly, TAK-003 demonstrated overall protection in dengue-naive participants, thus representing an advancement in dengue vaccinology.

Following a recommendation from the WHO Strategic Advisory Group of Experts on Immunization that the live-attenuated, recombinant, tetravalent dengue vaccine CYD-TDV (which is based on a yellow fever virus backbone) should not be administered to DENV-naive individuals owing to higher risk of severe disease if they become infected with DENV after vaccination,[10,11] long-term assessment of the efficacy and safety of dengue vaccines and vaccine candidates in this subpopulation has become an integral part of clinical development.[32] Unlike CYD-TDV, TAK-003 is a live-attenuated tetravalent DENV-2-based (PDK-53) recombinant vaccine[14] that elicits neutralising antibodies to DENV structural proteins of all four serotypes and cross-reactive humoral immune responses against DENV NS1 and cross-reactive, cell-mediated immune responses directed against DENV NS proteins.[28,29] The efficacy profile of TAK-003 also differs from that of CYD-TDV, and there has been no indication of increased risk of disease severity in dengue-naive participants following TAK-003 vaccination. These findings are most likely due to differences in vaccine construct and elicited immune responses.[33]

There are limitations to this analysis. First, the last 18 months of follow-up largely coincided with the COVID-19 pandemic, which saw a generally lower incidence of dengue cases reported during 2020 and 2021.[2] Second, not all participants might have passed through the peak dengue season in their respective areas during the months following year 4.

This study also shows the challenges of dengue vaccine development and evaluation. At the end of the long-term post-primary series follow-up, some data remained inconclusive. Specifically, any potential risk of enhanced disease due to DENV-3 and DENV-4 in baseline seronegative TAK-003 recipients could not be definitely excluded, precluding conclusive establishment of the efficacy and safety profiles of TAK-003 against these two serotypes in baseline seronegative individuals. Conservatively, this potential risk has been considered in the risk management plan and specific post-licensure activities are planned in agreement with competent authorities. Additionally, in view of the challenges of assessing serotype-level data in a pre-licensure setting, focused monitoring is planned in a large post-approval effectiveness study in dengue-endemic countries, in line with WHO guidance on dengue vaccine development.[17]

In summary, TAK-003 demonstrated cumulative long-term efficacy in preventing symptomatic dengue caused by all four DENV serotypes in previously exposed, and by DENV-1 and DENV-2 in dengue-naive, study participants

aged 4–16 years in eight dengue-endemic countries. This 4·5-year follow-up was conducted during a period of low DENV-4 incidence, and the data suggested a lack of efficacy of TAK-003 against DENV-3 in dengue-naive study participants. The vaccine also demonstrated a sustained high level of protection against hospitalised dengue and has the potential to reduce the burden associated with dengue. In determining the benefit–risk profile of TAK-003, public health officials will need to consider the balance of these benefits and the remaining knowledge gaps, along with a multitude of factors such as the growing burden of dengue, the limited options for dengue prevention, and the practical implementation of vaccination programmes.

Contributors

DY, HR, XS-L, CS, PL, CB-T, LB, PK, LMV, MTA, LR, VW, RD, LKF, VPW, EDM Jr, ADF, DG, KL, ALO, and FE were the investigators. SB, MR, OZ, DW, and IL designed the study. SB, VT, and NF managed the trial. YH, IE, and ST reviewed the data. SB, MR, OZ, EL, VT, IL, NF, and DW analysed and interpreted the data. VT managed the publication. All authors had full access to the presented data, provided critical input during manuscript preparation, and read and approved the manuscript for submission. The medical writers (Jenny Engelmoer, Sula Communications, The Netherlands and Adele Blair, Excel Medical Affairs) and SB, MR, OZ, EL, VT, IL, NF, and DW had full access to all the analyses and vouch for the accuracy and completeness of the data. DY, HR, XS-L, CS, PL, CB-T, LB, PK, LMV, MTA, LR, VW, RD, LKF, VPW, EDM Jr, ADF, DG, KL, ALO, FE, and EL verified the raw data.

Declaration of interests

VT, SB, ST, IE, YH, EL, MR, OZ, NF, IL, and DW are, or were, employees of Takeda and hold, or held, stock or stock options in Takeda. PK, CB-T, and XS-L report receiving research grants from Takeda. PK reports receiving research grants from Takeda and funding from Takeda for attending meetings. EDM Jr reports participating in an advisory board for Takeda. DY, HR, CS, PL, LB, MTA, VW, RD, LKF, LR, LMV, VPW, ADF, DG, KL, ALO, and FE declare no competing interests.

Data sharing

The datasets, including the redacted study protocol, redacted statistical analysis plan, and individual participants' data supporting the results of the completed study, will be made available within 3 months from initial request to researchers who provide a methodologically sound proposal. The data will be provided after its de-identification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymisation. Data requests should follow the process described in the Data Sharing section on https://clinicaltrials.takeda.com/ and https://vivli.org/ourmember/takeda/.

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