Dengue vaccine (TAK-003) GRADE tables for consideration by the Strategic Advisory Group of Experts (SAGE) on Immunization

Overarching question: The overarching question to be addressed when preparing the evidence to recommendations table is proposed below:

Should TAK-003 be recommended for introduction into national immunization programmes in a 2-dose schedule, to immunocompetent individuals (4-60 years of age) in dengue-endemic countries to mitigate the dengue burden of disease?

Contents

Summary

Table	Initial rating	Limitation in study design	Inconsistency	Indirectness	Imprecision	Publication bias	Large effect	Dose-response	Antagonistic bias& confounding	Final rating
GRADE TABLE 1a: Efficacy in children (any serostatus) against VCD (any serotype)	4	N/A	N/A	Very serious	N/A	N/A	N/A	N/A	N/A	Limited confidence ⊕⊕
GRADE TABLE 1b: Efficacy in children (any serostatus) against hospitalized VCD (any serotype)	4	Serious	N/A	Very serious	N/A	N/A	N/A	N/A	N/A	Very low confidence ⊕
GRADE TABLE 1c: Efficacy in seropositive children against VCD (any serotype)	4	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	High confidence ⊕⊕⊕⊕
GRADE TABLE 1d: Efficacy in seropositive children against hospitalized VCD (any serotype)	4	Serious	N/A	N/A	N/A	N/A	N/A	N/A	N/A	Moderate confidence ⊕⊕⊕
GRADE TABLE 1e: Efficacy in seronegative children against VCD (any serotype)	4	N/A	N/A	Very serious	N/A	N/A	N/A	N/A	N/A	Limited confidence ⊕⊕
GRADE TABLE 1f: Efficacy in seronegative children against hospitalized VCD (any serotype)	4	Serious	N/A	Very serious	N/A	N/A	N/A	N/A	N/A	Very low confidence ⊕
GRADE TABLE 2a: Efficacy in seropositive children against VCD (DENV 1)	4	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	High confidence ⊕⊕⊕⊕
GRADE TABLE 2b: Efficacy in seropositive children against hospitalized VCD (DENV 1)	4	Serious	N/A	N/A	N/A	N/A	Applicable	N/A	N/A	High confidence ⊕⊕⊕⊕
GRADE TABLE 2c: Efficacy in seronegative children against VCD (DENV 1)	4	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	High confidence ⊕⊕⊕⊕
GRADE TABLE 2d: Efficacy in seronegative children against hospitalized VCD (DENV 1)	4	Serious	N/A	N/A	N/A	N/A	Applicable	N/A	N/A	High confidence ⊕⊕⊕⊕
GRADE TABLE 3a: Efficacy in seropositive children against VCD (DENV 2)	4	N/A	N/A	N/A	N/A	N/A	[Applicable]	N/A	N/A	High confidence ⊕⊕⊕⊕
GRADE TABLE 3b: Efficacy in seropositive children against hospitalized VCD (DENV 2)	4	Serious	N/A	N/A	N/A	N/A	Applicable	N/A	N/A	High confidence ⊕⊕⊕⊕
GRADE TABLE 3c: Efficacy in seronegative children against VCD (DENV 2)	4	N/A	N/A	N/A	N/A	N/A	[Applicable]	N/A	N/A	High confidence ⊕⊕⊕⊕
GRADE TABLE 3d: Efficacy in seronegative children against hospitalized VCD (DENV 2)	4	Serious	N/A	N/A	N/A	N/A	Applicable	N/A	N/A	High confidence ⊕⊕⊕⊕
GRADE TABLE 4a: Efficacy in seropositive children against VCD (DENV 3)	4	N/A	N/A	Serious	N/A	N/A	Applicable	N/A	N/A	High confidence ⊕⊕⊕⊕
GRADE TABLE 4b: Efficacy in seropositive children against hospitalized VCD (DENV 3)	4	Serious	N/A	Serious	N/A	N/A	Applicable	N/A	N/A	Moderate confidence ⊕⊕⊕
GRADE TABLE 4c: Efficacy in seronegative children against VCD (DENV 3)	4	N/A	N/A	Serious	Very serious	N/A	N/A	N/A	N/A	Very low confidence ⊕

GRADE TABLE 4d: Efficacy in seronegative children against hospitalized VCD (DENV 3)	4	Serious	N/A	Serious	Very serious	N/A	N/A	N/A	N/A	Very low confidence ⊕
GRADE TABLE 5a: Efficacy in seropositive children against VCD (DENV 4)	4	N/A	N/A	N/A	N/A	N/A	[Applicable]	N/A	N/A	High confidence ⊕⊕⊕⊕
GRADE TABLE 5b: Efficacy in seropositive children against hospitalized VCD (DENV 4	4	Serious	N/A	N/A	Serious	N/A	N/A	N/A	N/A	Limited confidence ⊕⊕
GRADE TABLE 5c: Efficacy in seronegative children against VCD (DENV 4)	4	N/A	N/A	Serious	Very serious	N/A	N/A	N/A	N/A	Very low confidence ⊕
GRADE TABLE 5d: Efficacy in seronegative children against hospitalized VCD (DENV 4)	4	Serious	N/A	Serious	Very serious	N/A	N/A	N/A	N/A	Very low confidence ⊕
GRADE TABLE 6a: Efficacy in children (any serostatus) against DHF/severe Dengue	4	Serious	N/A	N/A	Very serious	N/A	N/A	N/A	N/A	Very low confidence ⊕
GRADE TABLE 6b: Efficacy in seropositive children against DHF/severe Dengue	4	Serious	N/A	N/A	Serious	N/A	N/A	N/A	N/A	Limited confidence ⊕⊕
GRADE TABLE 7a: Efficacy in adolescents and adults (any serostatus) against VCD (any serotype)	4	Serious	N/A	Very serious	N/A	N/A	N/A	N/A	N/A	Very low confidence ⊕
GRADE TABLE 8a: Safety in children and adults (any serostatus) regarding non-Dengue SAEs	4	N/A	N/A	N/A	Serious	N/A	N/A	N/A	N/A	Moderate confidence ⊕⊕⊕
GRADE TABLE 8b: Safety in seronegative children regarding DHF/ Severe Dengue	4	Serious	N/A	N/A	Very serious	N/A	N/A	N/A	N/A	Very low confidence ⊕

Part 1. GRADE questions on the efficacy of TAK-003 in children 4-16 years of age in endemic countries (Tables 1a – 6b)

GRADE TABLE 1a: Efficacy in immunocompetent children (any serostatus) against virologically confirmed disease (VCD) caused by any serotype.

Population: Immunocompetent children 4-16 years in endemic countries
Intervention: 2 doses of TAK-003 administered 3 months apart
Comparison: Placebo
Outcome: Virologically confirmed dengue (VCD) caused by any serotype

What is the efficacy of 2 doses of TAK-003 in preventing **virologically confirmed dengue (VCD) caused by any serotype** compared to placebo in immunocompetent children in endemic countries 4-16 years of age?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		1 RCT[1] [1]	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	Very serious[2]	-2
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable[3]	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			2
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **limited level of confidence** that the true effect lies close to the estimate of the effect on health outcomes.

[1] TAK-003 was evaluated in a Phase III safety and efficacy randomised controlled trial (n=20,099 healthy participants ages 4-16 years randomised 2:1 to receive two doses of TAK-003 or placebo three months apart) at 26 sites in eight dengue-endemic countries (Brazil, Colombia, Dominican Republic, Nicaragua, Panama, Philippines, Sri Lanka, Thailand). The trial design and duration of follow-up were compliant with WHO guidelines. Overall vaccine efficacy (VE) against VCD caused by any serotype was 80.2% (95% confidence interval (CI), 73.3-85.3) 30 days to 12 months post 2nd dose. The overall VE against VCD during the extended follow-up period (57 months following the first dose) was 61.2% (95% CI 56.0- 65.8) [ClinicalTrials.gov NCT02747927, results forthcoming].

[2] Two points were deducted for indirectness, given that no statistically significant efficacy against VCD caused by DENV3 or DENV4 could be demonstrated, but the numbers of cases of DENV3 and DENV4 were low overall with heterogeneity between trial sites.

[3] An overall large effect is noted (VE point estimate of 61.2% 57 months following the first dose). However, the score was not upgraded by one point given concerns around indirectness.

	Conclusion	The setting of the trial was characterized by the dominance of serotypes 1 and 2 and data on the efficacy in settings where serotypes 3 and 4 are circulating are limited. TAK-003 demonstrates statistically significant efficacy against overall VCD in trial participants 4-16 years of age in the trial setting though uncertainty remains around efficacy against VCD in settings where serotypes 3 and 4 predominate.

GRADE TABLE 1b: Efficacy in children (any serostatus) against hospitalized VCD (any serotype).

Population: Immunocompetent children 4-16 years in endemic countries
Intervention: 2 doses of TAK-003 administered 3 months apart
Comparison: Placebo
Outcome: Hospitalized VCD caused by any serotype

What is the efficacy of 2 doses of TAK-003 in preventing **hospitalized VCD caused by any serotype** compared to placebo in immunocompetent children 4-16 years of age in endemic countries?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		1 RCT[4] [1]	4
	Factors decreasing confidence	Limitation in study design	Serious[5]	-1
		Inconsistency	None serious	0
		Indirectness	Very serious[6]	-2
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable[7]	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of certainty of the evidence			1

[4] TAK-003 was evaluated in a Phase III safety and efficacy randomised controlled trial (n=20,099 healthy participants ages 4-16 randomised 2:1 to receive two doses of TAK-003 or placebo three months apart) at 26 sites in eight dengue-endemic countries. Overall vaccine efficacy (VE) against VCD leading to hospitalization caused by any serotype was 90.4% (95% confidence interval: 82.6-94.7) (30 days post second dose to 18 months after second dose, per protocol analysis, secondary trial endpoint). The overall VE against hospitalization 57 months after the first dose was 84.1% (77.8-88.6) [ClinicalTrials.gov NCT02747927, results forthcoming].

[5] There were no defined thresholds for hospitalisation (determined by the treating clinician) and a difference in hospitalization rates between the trial sites. All participants with a positive rapid antigen test for non-structural protein 1 (NS1) in serum were hospitalised for observation at the DEN-301 sites in Sri Lanka (68% hospitalisation rate, or 70 of 103 VCD cases as compared to 72 of 457 VCD cases across other sites), and platelet count and ultrasound examination for plasma leakage were conducted more frequently, leading to a higher proportion of patients being classified as having dengue haemorrhagic fever (DHF). A sensitivity analysis was conducted comparing results with and without Sri Lanka included, and the vaccine was still highly efficacious against hospitalised VCD overall (79.3% VE [95% CI 63.5-88.2] with Sri Lanka data vs 73.5% VE (95% CI 42.9-87.7) without Sri Lanka data among baseline seronegative participants and 85.9% VE [95% CI 78.7-90.7] with Sri Lanka data vs 83.3% VE [95% CI 71.4-90.2] without Sri Lanka data among seropositive participants 57 months after first dose).

[6] One point was deducted for indirectness given that efficacy could not be demonstrated against hospitalized VCD caused by DENV3 or DENV4, given the low representation of these serotypes overall and the wide variation in prevalence between sites.

[7] Although an overall large effect (84.1% overall VE against VCD leading to hospitalization caused by any serotype 57 months post-dose 1) was observed, two points were not added given concerns around indirectness.

Summary of Findings	Statement on the certainty of evidence	Evidence supports a **very low level of confidence** that the true effect lies close to the estimate of the effect on health outcome
	Conclusion	The setting of the trial was characterized by the dominance of serotypes 1 and 2 and data on the efficacy in settings where serotypes 3 and 4 are circulating are limited. TAK-003 demonstrates overall statistically significant efficacy against hospitalized VCD over 18 months among trial participants 4-16 years of age, though uncertainty remains around efficacy in settings where mainly serotypes 3 and 4 circulate.

GRADE TABLE 1c: Efficacy in seropositive children against VCD (any serotype).

Population: Baseline seropositive immunocompetent children and adolescents 4-16 years in endemic countries
Intervention: 2 doses of TAK-003 administered 3 months apart
Comparison: Placebo
Outcome: VCD caused by any serotype

What is the efficacy of 2 doses of TAK-003 in preventing **VCD caused by any serotype** compared to placebo **in baseline seropositive** immunocompetent children 4-16 years of age in endemic countries?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		1 RCT[8] [1]	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Applicable[9]	(+1)
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			4
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **high level of confidence** that the true effect lies close to the estimate of the effect on health outcome
	Conclusion			TAK-003 demonstrates statistically significant efficacy against VCD over 18 months among trial participants 4-16 years of age who were seropositive at baseline.

[8] TAK-003 was evaluated in a Phase III safety and efficacy randomised controlled trial (n=20,099 healthy participants ages 4-16 randomised 2:1 to receive two doses of TAK-003 or placebo three months apart) at 26 sites in eight dengue-endemic countries. Overall vaccine efficacy against VCD among seropositive individuals was 76.1% (95% CI: 68.5-81.9) (30 days post second dose to 18 months after second dose, per protocol analysis, secondary trial endpoint) and 64.2% (95% CI 58.4- 69.2) 57 months after the first dose (exploratory endpoint). Over 57 months, TAK-003 prevents 5064 cases per 100,000 vaccinated. (Nov 2022 Takeda presentation) [ClinicalTrials.gov NCT02747927, results forthcoming].

[9] A moderately large effect is noted (64.2% 57 months after the first dose). An addition of 1 point is applicable but is shown in parentheses since the total score is 4 and the addition is not counted towards the final score.

GRADE TABLE 1d: Efficacy in seropositive children against hospitalized VCD (any serotype).

Population: Baseline seropositive immunocompetent children 4-16 years in endemic countries
Intervention: 2 doses of TAK-003 administered 3 months apart
Comparison: Placebo
Outcome: Hospitalized VCD caused by any serotype

What is the efficacy of 2 doses of TAK-003 in preventing **hospitalized VCD caused by any serotype compared to placebo in baseline seropositive** immunocompetent children 4-16 years of age in endemic countries?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		1 RCT[10] [1]	4
	Factors decreasing confidence	Limitation in study design	Serious[11]	-1
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable[12]	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			3

[10] TAK-003 was evaluated in a Phase III safety and efficacy randomised controlled trial (n=20,099 healthy participants ages 4-16 randomised 2:1 to receive two doses of TAK-003 or placebo three months apart) at 26 sites in eight dengue-endemic countries. Overall vaccine efficacy (VE) against VCD leading to hospitalization caused by any serotype in baseline seropositive immunocompetent children was 91.4% (95% CI 81.7, 95.9) (30 days post second dose to 18 months after second dose, per protocol analysis), and VE against VCD leading to hospitalization caused by any serotype in baseline seropositive immunocompetent children was 85.9% (95% CI 78.7, 90.7) 57 months after dose 1 [ClinicalTrials.gov NCT02747927, results forthcoming].
[11] There were no defined thresholds for hospitalisation (determined by the treating clinician) with heterogeneity in the proportion of hospitalized cases between trial sites. All participants with a positive rapid antigen test for non-structural protein 1 (NS1) in serum were hospitalised for observation at the DEN-301 sites in Sri Lanka (68% hospitalisation rate, or 70 of 103 VCD cases as compared to 72 of 457 VCD cases across other sites), and platelet count and ultrasound examination for plasma leakage were conducted more frequently, leading to a higher proportion of patients being classified as having dengue haemorrhagic fever (DHF). A sensitivity analysis was conducted comparing results with and without Sri Lanka included, and the vaccine was still highly efficacious against hospitalised VCD among baseline seronegative children. The overall VE against VCD leading to hospitalization among children who were seropositive at baseline was 85.9% (95% CI 82.6-94.7) including Sri Lanka data (or 83.3% [95% CI 71.4-90.2] excluding Sri Lanka data) during the extended follow-up period (57 months following the first dose), during which time, TAK-003 prevents an estimated 1780 cases of hospitalized VCD among seropositive individuals per 100,000 vaccinated (Takeda Nov 2022 presentation).
[8] A large effect is noted (85.9% VE against VCD caused by any serotype leading to hospitalization 57 months post dose 1). An addition of 2 points is applicable but is shown in parentheses since the total score is 4 and the addition is not fully counted towards the final score.

Summary of Findings	Statement on the certainty of evidence	Evidence supports a **moderate level of confidence** that the true effect lies close to the estimate of the effect on health outcome.
	Conclusion	TAK-003 demonstrates statistically significant efficacy against hospitalized VCD among trial participants 4-16 years of age who are seropositive at baseline.

GRADE TABLE 1e: Efficacy in seronegative children against VCD (any serotype).

Population: Baseline seronegative immunocompetent children 4-16 years in endemic countries
Intervention: 2 doses of TAK-003 administered 3 months apart
Comparison: Placebo
Outcome: VCD caused by any serotype

What is the efficacy of 2 doses of TAK-003 in preventing **VCD caused by any serotype compared to placebo in baseline seronegative** immunocompetent children 4-16 years of age in endemic countries?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		1 RCT[13] [1]	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	Very serious[14]	-2
		Imprecision	None serious	0
		Publication bias	Not applicable	0
	Factors increasing confidence	Large effect	Not applicable[15]	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of certainty of the evidence			2
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **limited level of confidence** that the true effect lies close to the estimate of the effect on the health outcome.

[13] TAK-003 was evaluated in a Phase III safety and efficacy randomised controlled trial (n=20,099 healthy participants ages 4-16 randomised 2:1 to receive two doses of TAK-003 or placebo three months apart) at 26 sites in eight dengue-endemic countries. Overall vaccine efficacy (VE) against VCD caused by any serotype in baseline seronegative children was 66.2% (95% CI 49.1-77.5) (30 days post-second dose to 18 months after the second dose, per protocol analysis). Overall, VE against VCD caused by any serotype among baseline seronegative children 57 months post dose 1 was 53.5% (95% CI 41.6-62.9), and TAK-003 prevented an estimated 4393 cases of VCD among seronegative subjects for every 100,000 vaccinated during this time period (Takeda Nov 2022 presentation) [ClinicalTrials.gov NCT02747927, results forthcoming].
[14] Two points were deducted considering the lack of demonstrated vaccine efficacy against VCD caused by DENV3 or DENV4 in baseline seronegative participants and the low representation of these serotypes in the study with a wide variation in prevalence across sites.
[15] Although a moderately large effect was observed (VE point estimate of 53.5% against VCD caused by any serotype in baseline seronegative children 57 months after dose 1), 1 point was not added given concerns around indirectness.

	Conclusion	TAK-003 demonstrates statistically significant efficacy against VCD among trial participants 4-16 years of age who were seronegative at baseline, in the setting of the trial, though uncertainty remains around efficacy against VCD in settings where mainly serotypes 3 and 4 circulate.

GRADE TABLE 1f: Efficacy in seronegative children against hospitalized VCD (any serotype).

Population: Baseline seronegative immunocompetent children 4-16 years in endemic countries
Intervention: 2 doses of TAK-003 administered 3 months apart
Comparison: Placebo
Outcome: Hospitalized VCD caused by any serotype

What is the efficacy of 2 doses of TAK-003 in preventing **hospitalized VCD caused by any serotype compared to placebo in baseline seronegative** immunocompetent children 4-16 years of age in endemic countries?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		1 RCT[16] [1]	4
	Factors decreasing confidence	Limitation in study design	Serious[17]	-1
		Inconsistency	None serious	0
		Indirectness	Very serious[18]	-2
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable[19]	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			1

[16] TAK-003 was evaluated in a Phase III safety and efficacy randomised controlled trial (n=20,099 healthy participants ages 4-16 randomised 2:1 to receive two doses of TAK-003 or placebo three months apart) at 26 sites in eight dengue-endemic countries. Overall vaccine efficacy (VE) against VCD leading to hospitalization caused by any serotype in baseline seronegative children was 88.1% (95% CI 68.5-95.5) (30 days post second dose to 18 months after the second dose, per protocol analysis), and 79.3% (95% CI 63.5- 88.2) 57 months post dose 1 [ClinicalTrials.gov NCT02747927, results forthcoming].

[17] There were no defined thresholds for hospitalisation (determined by the treating clinician) with heterogeneity between sites. All participants with a positive rapid antigen test for non-structural protein 1 (NS1) in serum were hospitalised for observation at the DEN-301 sites in Sri Lanka (68% hospitalisation rate, or 70 of 103 VCD cases as compared to 72 of 457 VCD cases across other sites), and platelet count and ultrasound examination for plasma leakage were conducted more frequently, leading to a higher proportion of patients being classified as having dengue haemorrhagic fever (DHF). A sensitivity analysis was conducted comparing results with and without Sri Lanka included, and the vaccine was still highly efficacious against hospitalised VCD among baseline seropositive children. The overall VE against VCD leading to hospitalization caused by any serotype in baseline seronegative children was 79.3% (95% CI 63.5-88.2) including Sri Lanka data (or 73.5% [95% CI 42.9-87.7] excluding Sri Lanka data) during the extended follow-up period (57 months following the first dose), during which time, TAK-003 prevents an estimated 1780 cases of hospitalized VCD among seronegative subjects per 100,000 vaccinated (Takeda Nov 2022 presentation).

[18] Two points were deducted considering the lack of demonstrated vaccine efficacy against hospitalized VCD caused by DENV3 or DENV4 in baseline seronegative participants and the low representation of DENV3 and DENV4 cases overall and wide variation in the prevalence of these serotypes across sites.

[19] Although a large effect was observed (point estimate of 79.3% VE against VCD leading to hospitalization caused by any serotype 57 months post-dose 1 among baseline seronegative children), the score was not upgraded given concerns around indirectness.

Summary of Findings	Statement on the certainty of evidence	Evidence supports a **very low level of confidence** that the true effect lies close to the estimate of the effect on health outcome
	Conclusion	TAK-003 demonstrates statistically significant efficacy against hospitalized VCD among trial participants 4-16 years of age who are seronegative at baseline in the setting of the trial where serotypes 1 and 2 were the dominantly circulating serotypes, though uncertainty remains around efficacy against hospitalized VCD in settings where mainly serotypes 3 and 4 circulate.

GRADE TABLE 2a: Efficacy in seropositive children against VCD (DENV1)

Population: Baseline seropositive immunocompetent children 4-16 years in endemic countries
Intervention: 2 doses of TAK-003 administered 3 months apart
Comparison: Placebo
Outcome: VCD caused by DENV 1

What is the efficacy of 2 doses of TAK-003 in preventing **virologically confirmed dengue (VCD) caused by DENV1 compared to placebo** in baseline seropositive immunocompetent children 4-16 years of age in endemic countries?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		1 RCT[20] [1]	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Applicable[21]	(+1)
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			4
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **high level of confidence** that the true effect lies close to the estimate of the effect on the health outcome.
	Conclusion			TAK-003 demonstrates statistically significant efficacy against VCD caused by DENV1 among trial participants 4-16 years of age who were seropositive at baseline.

[20] TAK-003 was evaluated in a Phase III safety and efficacy randomised controlled trial (n=20,099 healthy participants ages 4-16 randomised 2:1 to receive two doses of TAK-003 or placebo three months apart) at 26 sites in eight dengue-endemic countries. Overall vaccine efficacy (VE) against VCD caused by DENV1 in baseline seropositive children was 56.1% (95% CI 44.6, 65.2) in the safety set (57 months post dose 1) [ClinicalTrials.gov NCT02747927, results forthcoming].

[21] A moderate effect size was noted (point estimate VE 56.1% against VCD caused by DENV1 in baseline seropositive children 57 months post dose 1) so one point would have been added, although currently, the score is not eligible for an upgrade at the maximum score.

GRADE TABLE 2b: Efficacy in seropositive children against hospitalized VCD (DENV1).

Population: Baseline seropositive immunocompetent children 4-16 years in endemic countries

Intervention: 2 doses of TAK-003 administered 3 months apart

Comparison: Placebo

Outcome: Hospitalized VCD caused by DENV 1

What is the efficacy of 2 doses of TAK-003 in preventing **hospitalized VCD caused by DENV1** compared to placebo in baseline seropositive immunocompetent children 4-16 years of age in endemic countries?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		1 RCT[22] [1]	4
	Factors decreasing confidence	Limitation in study design	Serious[23]	-1
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Applicable[24]	+1
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of certainty of the evidence			4
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **high level of confidence** that the true effect lies close to the estimate of the effect on the health outcome.

[22] TAK-003 was evaluated in a Phase III safety and efficacy randomised controlled trial (n=20,099 healthy participants ages 4-16 randomised 2:1 to receive two doses of TAK-003 or placebo three months apart) at 26 sites in eight dengue-endemic countries. Overall vaccine efficacy (VE) against hospitalized VCD caused by DENV1 among individuals who were seropositive at baseline was 66.8% (95% CI 37.4- 82.3) 57 months after the first dose [ClinicalTrials.gov NCT02747927, results forthcoming].

[23] There were no defined thresholds for hospitalisation (determined by the treating clinician) with heterogeneity in the proportion of cases hospitalized between trial sites. All participants with a positive rapid antigen test for non-structural protein 1 (NS1) in serum were hospitalised for observation at the DEN-301 sites in Sri Lanka (68% hospitalisation rate, or 70 of 103 VCD cases as compared to 72 of 457 VCD cases across other sites), and platelet count and ultrasound examination for plasma leakage were conducted more frequently, leading to a higher proportion of patients being classified as having dengue haemorrhagic fever (DHF).

[24] A moderately large effect is noted (VE point estimate 66.8% against hospitalized VCD caused by DENV1 among baseline seropositive individuals 57 months after the first dose), so one point was added.

	Conclusion	TAK-003 demonstrates statistically significant efficacy against virologically-confirmed dengue leading to hospitalization caused by DENV1 among trial participants 4-16 years of age who were seropositive at baseline.

GRADE TABLE 2c: Efficacy in seronegative children against VCD (DENV1).

Population: Baseline seronegative immunocompetent children 4-16 years in endemic countries
Intervention: 2 doses of TAK-003 administered 3 months apart
Comparison: Placebo
Outcome: VCD caused by DENV 1

What is the efficacy of 2 doses of TAK-003 in preventing **VCD caused by DENV1** compared to placebo **in baseline seronegative** immunocompetent children 4-16 years of age in endemic countries?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		1 RCT[25] [1]	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable[26]	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			4
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **high level of confidence** that the true effect lies close to the estimate of the effect on the health outcome.
	Conclusion			TAK-003 demonstrates statistically significant efficacy against VCD caused by DENV1 among trial participants 4-16 years of age who were seronegative at baseline.

[25] TAK-003 was evaluated in a Phase III safety and efficacy randomised controlled trial (n=20,099 healthy participants ages 4-16 randomised 2:1 to receive two doses of TAK-003 or placebo three months apart) at 26 sites in eight dengue-endemic countries. Vaccine efficacy against VCD caused by DENV1 among seronegative children was 45.4% (95% CI 26.1- 59.7) 57 months after dose 1 [ClinicalTrials.gov NCT02747927, results forthcoming].

GRADE TABLE 2d: Efficacy in seronegative children against hospitalized VCD (DENV1)

Population: Baseline seronegative immunocompetent children 4-16 years in endemic countries
Intervention: 2 doses of TAK-003 administered 3 months apart
Comparison: Placebo
Outcome: Hospitalized VCD caused by DENV 1

What is the efficacy of 2 doses of TAK-003 in preventing **hospitalized VCD caused by DENV1 compared to placebo in baseline seronegative** immunocompetent children 4-16 years of age in endemic countries?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		1 RCT[27] [1]	4
	Factors decreasing confidence	Limitation in study design	Serious[28]	-1
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Applicable[29]	+1
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			4
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **high level of confidence** that the true effect lies close to the estimate of the effect on the health outcome.

[27] TAK-003 was evaluated in a Phase III safety and efficacy randomised controlled trial (n=20,099 healthy participants ages 4-16 randomised 2:1 to receive two doses of TAK-003 or placebo three months apart) at 26 sites in eight dengue-endemic countries. Overall vaccine efficacy (VE) against VCD leading to hospitalization caused by DENV1 in baseline seronegative children was 78.4% (95% CI 43.9-91.7) including Sri Lanka data (or 78.9% [95% CI 40.1-92.6] excluding Sri Lanka data) during the extended follow-up period (57 months following the first dose). There were only 20 cases of hospitalization caused by VCD caused by DENV1 among baseline seronegative individuals over 57 months [ClinicalTrials.gov NCT02747927, results forthcoming].
[28] There were no defined thresholds for hospitalisation (determined by the treating clinician) with heterogeneity in the proportion of cases hospitalized between sites. All participants with a positive rapid antigen test for non-structural protein 1 (NS1) in serum were hospitalised for observation at the DEN-301 sites in Sri Lanka (68% hospitalisation rate, or 70 of 103 VCD cases as compared to 72 of 457 VCD cases across other sites), and platelet count and ultrasound examination for plasma leakage were conducted more frequently, leading to a higher proportion of patients being classified as having dengue haemorrhagic fever (DHF).
[29] A moderately large effect is noted (VE point estimate of 78.4% against VCD leading to hospitalization caused by DENV1 in baseline seronegative individuals 57 months after the first dose), hence one point was added.

	Conclusion	TAK-003 demonstrates statistically significant efficacy against hospitalized VCD caused by DENV1 among trial participants 4-16 years of age who are seronegative at baseline.

GRADE TABLE 3a: Efficacy in seropositive children against VCD (DENV2)

Population: Baseline seropositive immunocompetent children 4-16 years c countries
Intervention: 2 doses of TAK-003 administered 3 months apart
Comparison: Placebo
Outcome: VCD caused by DENV 2

What is the efficacy of 2 doses of TAK-003 in preventing **VCD caused by DENV2** compared to placebo in baseline seropositive immunocompetent children 4-16 years of age in endemic countries?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		1 RCT[30] [1]	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Applicable[31]	(+2)
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			4
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **high level of confidence** that the true effect lies close to the estimate of the effect on health outcomes.
	Conclusion			TAK-003 demonstrates statistically significant efficacy against VCD caused by DENV2 among trial participants 4-16 years of age who were seropositive at baseline.

[30] TAK-003 was evaluated in a Phase III safety and efficacy randomised controlled trial (n=20,099 healthy participants ages 4-16 randomised 2:1 to receive two doses of TAK-003 or placebo three months apart) at 26 sites in eight dengue-endemic countries. Overall vaccine efficacy (VE) against VCD caused by DENV2 was 80.4% (95% CI 73.1- 85.7) among baseline seropositive individuals 57 months after dose 1 [ClinicalTrials.gov NCT02747927, results forthcoming].

[31] A large effect is noted (VE point estimate of 80.4% against VCD caused by DENV2 57 months after dose 1). Two points would have been added, although currently, the score is not eligible for an upgrade at the maximum score.

GRADE TABLE 3b: Efficacy in seropositive children against hospitalized VCD (DENV2).

Population: Baseline seropositive immunocompetent children 4-16 years in endemic countries
Intervention: 2 doses of TAK-003 administered 3 months apart
Comparison: Placebo
Outcome: Hospitalized VCD caused by DENV 2

What is the efficacy of 2 doses of TAK-003 in preventing **hospitalized VCD caused by DENV2** compared to placebo in baseline seropositive immunocompetent children 4-16 years of age in endemic countries?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		1 RCT[32] [1]	4
	Factors decreasing confidence	Limitation in study design	Serious[33]	-1
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Applicable[34]	(+2)
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			4
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **high level of confidence** that the true effect lies close to the estimate of the effect on the health outcome.

[32] TAK-003 was evaluated in a Phase III safety and efficacy randomised controlled trial (n=20,099 healthy participants ages 4-16 randomised 2:1 to receive two doses of TAK-003 or placebo three months apart) at 26 sites in eight dengue-endemic countries. Overall vaccine efficacy (VE) against VCD leading to hospitalization caused by DENV2 was 95.8% (95% CI 89.6- 98.3) among baseline seropositive participants (64 total cases) 57 months after the first dose [ClinicalTrials.gov NCT02747927, results forthcoming].

[33] There were no defined thresholds for hospitalisation (determined by the treating clinician) and heterogeneity in the proportion of cases hospitalized between trial sites. All participants with a positive rapid antigen test for non-structural protein 1 (NS1) in serum were hospitalised for observation at sites in Sri Lanka (68% hospitalisation rate, or 70 of 103 VCD cases as compared to 72 of 457 VCD cases across other sites), and platelet count and ultrasound examination for plasma leakage were conducted more frequently, leading to a higher proportion of patients being classified as dengue haemorrhagic fever (DHF).

[34] A large effect is noted regardless of baseline serostatus (VE point estimate of 95.8% against VCD leading to hospitalization caused by DENV2 in baseline seropositive individuals), so two points would have been added, but only one point was awarded as 4 is the maximum score.

	Conclusion	TAK-003 demonstrates statistically significant efficacy against hospitalized VCD caused by DENV2 among trial participants 4-16 years of age who were seropositive at baseline.

GRADE TABLE 3c: Efficacy in seronegative children against VCD (DENV2).

Population: Baseline seronegative immunocompetent children 4-16 years in endemic countries
Intervention: 2 doses of TAK-003 administered 3 months apart
Comparison: Placebo
Outcome: VCD caused by DENV 2

What is the efficacy of 2 doses of TAK-003 in preventing **virologically confirmed dengue (VCD) caused by DENV2** compared to placebo **in baseline seronegative** immunocompetent children 4-16 years of age in endemic countries?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		1 RCT[35] [1]	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Applicable[36]	(+2)
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			4
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **high level of confidence** that the true effect lies close to the estimate of the effect on the health outcome.
	Conclusion			TAK-003 demonstrates statistically significant efficacy against VCD caused by DENV2 among trial participants 4-16 years of age who were seronegative at baseline.

[35] TAK-003 was evaluated in a Phase III safety and efficacy randomised controlled trial (n=20,099 healthy participants ages 4-16 randomised 2:1 to receive two doses of TAK-003 or placebo three months apart) at 26 sites in eight dengue-endemic countries. Overall vaccine efficacy of 88.1% (95% CI 78.6-93.3) was estimated against VCD caused by DENV2 among seronegative children 57 months after first dose [ClinicalTrials.gov NCT02747927, results forthcoming].

[36] A large effect is noted (point estimate VE 88.1% against VCD caused by DENV2 among seronegative children 57 months after dose 1), so two points would have been added, although currently the score is not eligible for upgrade at the maximum score.

GRADE TABLE 3d: **Efficacy in seronegative children against hospitalized VCD (DENV2).**
Population: Baseline seronegative immunocompetent children 4-16 years in endemic countries
Intervention: 2 doses of TAK-003 administered 3 months apart
Comparison: Placebo
Outcome: Hospitalized VCD caused by DENV 2

What is the efficacy of 2 doses of TAK-003 in preventing **hospitalized VCD caused by DENV2 compared to placebo in baseline seronegative immunocompetent** children 4-16 years of age in endemic countries?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		1 RCT[37] [1]	4
	Factors decreasing confidence	Limitation in study design	Serious[38]	-1
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Applicable[39]	(+2)
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			4
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **high level of confidence** that the true effect lies close to the estimate of the effect on the health outcome.

[37] TAK-003 was evaluated in a Phase III safety and efficacy randomised controlled trial (n=20,099 healthy participants ages 4-16 randomised 2:1 to receive two doses of TAK-003 or placebo three months apart) at 26 sites in eight dengue-endemic countries. TAK-003 appears highly protective (100% VE, 95% CI NE, NE) against hospitalized VCD caused by DENV2 among seronegative children 57 months after the first dose – all 23 cases occurred in placebo recipients but there were very few hospitalized cases of VCD caused by DENV2 [ClinicalTrials.gov NCT02747927, results forthcoming].
[38] There were no defined thresholds for hospitalisation (determined by the treating clinician) and heterogeneity in the proportion of cases hospitalized between trial sites. All participants with a positive rapid antigen test for non-structural protein 1 (NS1) in serum were hospitalised for observation at the DEN-301 sites in Sri Lanka (68% hospitalisation, or 70 of 103 VCD cases as compared to 72 of 457 VCD cases across other sites), and platelet count and ultrasound examination for plasma leakage were conducted more frequently, leading to a higher proportion of patients classified as dengue haemorrhagic fever (DHF).
[39] A large effect is noted (VE point estimate 100% against hospitalized VCD caused by DENV2 among seronegative children 57 months after first dose, 23 cases of hospitalized VCD caused by DENV2 among baseline seronegative placebo recipients and 0 among TAK-003 recipients); two points would have been added but the maximum score is 4, so only one point was added.

	Conclusion	TAK-003 demonstrates statistically significant efficacy against VCD leading to hospitalization caused by DENV2 in trial participants 4-16 years of age who were seronegative at baseline.

GRADE TABLE 4a: Efficacy in seropositive children against VCD (DENV3).

Population: Baseline seropositive immunocompetent children 4-16 years in endemic countries
Intervention: 2 doses of TAK-003 administered 3 months apart
Comparison: Placebo
Outcome: VCD caused by DENV 3

What is the efficacy of 2 doses of TAK-003 in preventing **virologically confirmed dengue (VCD) caused by DENV3** compared to placebo in baseline seropositive immunocompetent children 4-16 years of age in endemic countries?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		1 RCT[40] [1]	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	Serious[41]	-1
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Applicable[42]	+1
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			4
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **high level of confidence** that the true effect lies close to the estimated effect on the health outcome.

[40] TAK-003 was evaluated in a Phase III safety and efficacy randomised controlled trial (n=20,099 healthy participants ages 4-16 randomised 2:1 to receive two doses of TAK-003 or placebo three months apart) at 26 sites in eight dengue-endemic countries. Overall vaccine efficacy (VE) against VCD caused by DENV3 was 52.3% (95% CI 36.7-64.0) among baseline seropositive trial participants in the safety set (57 months post dose 1) [ClinicalTrials.gov NCT02747927, results forthcoming].

[41] One point was deducted for indirectness given the heterogeneity in the number of cases of DENV3 between sites and the age distribution of these cases; most DENV3 cases occurred in the Philippines, where the age distribution of cases was lower than at other sites.

[42] There were very few cases of DENV3 during the study period (52 cases in total over 57 months), and the incidence of DENV3 in the TAK-003 group (36/2714, 1.0%) was similar to that in the placebo group (16/1832, 0.9%), with 52.3% VE (95% CI 36.7-64.0) among individuals who were seropositive at baseline 57 months after dose 1, so these data provide moderate confidence in the efficacy of TAK-003 against VCD caused by DENV3 among baseline seropositive individuals.

	Conclusion	TAK-003 demonstrates statistically significant efficacy against VCD caused by DENV3 among trial participants 4-16 years of age who were seropositive at baseline

GRADE TABLE 4b: Efficacy in seropositive children against hospitalized VCD (DENV3).

Population: Baseline seropositive immunocompetent children 4-16 years in endemic countries
Intervention: 2 doses of TAK-003 administered 3 months apart
Comparison: Placebo
Outcome: Hospitalized VCD caused by DENV 3

What is the efficacy of 2 doses of TAK-003 in preventing **hospitalized VCD caused by DENV3** compared to placebo in baseline seropositive immunocompetent children 4-16 years of age in endemic countries?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		1 RCT[43] [1]	4
	Factors decreasing confidence	Limitation in study design	Serious[44]	-1
		Inconsistency	None serious	0
		Indirectness	Serious[45]	-1
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Applicable[46]	+1
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			3
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **moderate level of confidence** that the true effect lies close to the estimate of the effect on health outcome given variability between baseline serostatus and low overall case numbers.

[43] TAK-003 was evaluated in a Phase III safety and efficacy randomised controlled trial (n=20,099 healthy participants ages 4-16 randomised 2:1 to receive two doses of TAK-003 or placebo three months apart) at 26 sites in eight dengue-endemic countries. The estimated vaccine efficacy (VE) against hospitalized VCD caused by DENV3 was 74.0% (38.6, 89.0) in baseline seropositive individuals (32 total cases) 57 months after dose one [ClinicalTrials.gov NCT02747927, results forthcoming].

[44] There were no defined thresholds for hospitalisation (determined by the treating clinician) and heterogeneity in the proportion of cases hospitalized between trial sites. All participants with a positive rapid antigen test for non-structural protein 1 (NS1) in serum were hospitalised for observation at the DEN-301 sites in Sri Lanka (68% hospitalisation rate, or 70 of 103 VCD cases as compared to 72 of 457 VCD cases across other sites), and platelet count and ultrasound examination for plasma leakage were conducted more frequently, leading to a higher proportion of patients being classified as having dengue haemorrhagic fever (DHF).

[45] One point was deducted for indirectness given the heterogeneity in the number of cases of DENV3 between sites and the age distribution of these cases; most DENV3 cases occurred in the Philippines, where the age distribution of cases was lower than at other sites.

[46] Point estimate of VE against hospitalized VCD caused by DENV3 in baseline seropositive children was 74% (95% CI 38.6, 89.0), so one point was added for effect size.

	Conclusion	TAK-003 demonstrates moderate efficacy against VCD leading to hospitalization caused by DENV3 among trial participants 4-16 years of age who were seropositive at baseline.

GRADE TABLE 4c: Efficacy in seronegative children against VCD (DENV3).

Population: Baseline seronegative immunocompetent children 4-16 years in endemic countries
Intervention: 2 doses of TAK-003 administered 3 months apart
Comparison: Placebo
Outcome: VCD caused by DENV 3

What is the efficacy of 2 doses of TAK-003 in preventing **virologically confirmed dengue (VCD) caused by DENV3** compared to placebo **in baseline seronegative** immunocompetent children 4-16 years of age in endemic countries?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		1 RCT[47] [1]	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	Serious[48]	-1
		Imprecision	Very serious[49]	-2
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			1
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **very low level of confidence** that the true effect lies close to the estimate of the effect on the health outcome.

[47] TAK-003 was evaluated in a Phase III safety and efficacy randomised controlled trial (n=20,099 healthy participants ages 4-16 randomised 2:1 to receive two doses of TAK-003 or placebo three months apart) at 26 sites in eight dengue-endemic countries. Vaccine efficacy against VCD caused by DENV3 among seronegative individuals 4-16 years of age was estimated to be -15.5% (95% CI -108.2- 35.9) 57 months after dose one [ClinicalTrials.gov NCT02747927, results forthcoming].

[48] One point was deducted for indirectness, as there were so few cases of VCD at a few sites caused by DENV3 in baseline seronegative participants in the DEN-301 trial population (52 total over a 57-month period). There was a great deal of heterogeneity in the number and age distribution of cases of DENV3 between sites. A high proportion of cases of DENV3 were from the Philippines where the proportion of subjects in the younger age groups was higher.

[49] Given the negative point estimate of efficacy (-15.5%) and the wide confidence interval, as well as the small number of cases of DENV3 over the 57-month study period (n=54), there is very weak evidence to support TAK-003's efficacy against VCD caused by DENV3 among baseline seronegative children.

	Conclusion	There is an absence of efficacy in seronegative vaccinated persons exposed to DENV3. Point estimates are negative with wide confidence intervals. A safety risk cannot be ruled out.

GRADE TABLE 4d: Efficacy in seronegative children against hospitalized VCD (DENV3).

Population: Baseline seronegative immunocompetent children 4-16 years in endemic countries
Intervention: 2 doses of TAK-003 administered 3 months apart
Comparison: Placebo
Outcome: Hospitalized VCD caused by DENV 3

What is the efficacy of 2 doses of TAK-003 in preventing **hospitalized VCD caused by DENV3 compared to placebo in baseline seronegative** immunocompetent children 4-16 years of age in endemic countries?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		1 RCT[50] [1]	4
	Factors decreasing confidence	Limitation in study design	Serious[51]	-1
		Inconsistency	None serious	0
		Indirectness	Serious[52]	-1
		Imprecision	Very serious[53]	-2
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			1[54]

[50] TAK-003 was evaluated in a Phase III safety and efficacy randomised controlled trial (n=20,099 healthy participants ages 4-16 randomised 2:1 to receive two doses of TAK-003 or placebo three months apart) at 26 sites in eight dengue-endemic countries. The estimated vaccine efficacy (VE) against hospitalized VCD caused by DENV3 was -87.9% (95% CI -573.4- 47.6) among baseline seronegative individuals (14 total cases) 57 months after dose one (and 15.3% [95% CI -254.4- 79.9] excluding Sri Lanka data) [ClinicalTrials.gov NCT02747927].

[51] There were no defined thresholds for hospitalisation (determined by the treating clinician) and heterogeneity in the proportion of cases hospitalized between trial sites. All participants with a positive rapid antigen test for non-structural protein 1 (NS1) in serum were hospitalised for observation at the DEN-301 sites in Sri Lanka (68% hospitalisation rate, or 70 of 103 VCD cases as compared to 72 of 457 VCD cases across other sites), and platelet count and ultrasound examination for plasma leakage were conducted more frequently, leading to a higher proportion of patients being classified as having dengue haemorrhagic fever (DHF).

[52] One point deducted for indirectness given the small number of cases of VCD leading to hospitalization caused by DENV3 among baseline seronegative participants in DEN-301 (14 cases over 57-month period) as well as the heterogeneity of numbers and age distribution of hospitalizations caused by DENV3 across sites. A high proportion of DENV3 cases were from the Philippines where the proportion of cases in the younger age groups was higher.

[53] VE against hospitalized VCD caused by DENV3 was -87.9% (95% CI -573.4- 47.6) among baseline seronegative individuals (14 total cases) 57 months after dose one and 15.3% (95% CI -254.4- 79.9) excluding Sri Lanka data). The imbalance of DENV-3 hospitalized VCD cases in seronegative subjects is confounded by clinical practice in Sri Lanka (see above); all six DENV3 cases in Sri Lanka in baseline seronegative subjects (all in TAK-003 group) were all hospitalized; however, there is still no demonstrable efficacy against hospitalized VCD caused by DENV3 among baseline seronegative individuals.

[54] While four points were deducted on account of limitations in study design, imprecision, and indirectness, 1 is the lowest possible score.

Summary of Findings	Statement on the certainty of evidence	Evidence supports **a very low level of confidence** that the true effect lies close to the estimate of the effect on the health outcome.
	Conclusion	There is an absence of efficacy in seronegative vaccinated persons exposed to DENV3. Point estimates are negative with wide confidence intervals. A safety risk cannot be ruled out.

GRADE TABLE 5a: Efficacy in seropositive children against VCD (DENV4).

Population: Baseline seropositive mmunocompetent children 4-16 years in endemic countries
Intervention: 2 doses of TAK-003 administered 3 months apart
Comparison: Placebo
Outcome: VCD caused by DENV 4

What is the efficacy of 2 doses of TAK-003 in preventing **virologically confirmed dengue (VCD) caused by DENV4 compared to placebo** in baseline seropositive immunocompetent children 4-16 years of age in endemic countries?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		1 RCT[55] [1]	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Applicable[56]	(+1)
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			4
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **high level of confidence** that the true effect lies close to the estimate of the effect on the health outcome.
	Conclusion			TAK-003 demonstrates moderate efficacy against VCD caused by DENV4 among trial participants 4-16 years of age who were seropositive at baseline.

[55] TAK-003 was evaluated in a Phase III safety and efficacy randomised controlled trial (n=20,099 healthy participants ages 4-16 randomised 2:1 to receive two doses of TAK-003 or placebo three months apart) at 26 sites in eight dengue-endemic countries. Overall vaccine efficacy (VE) against VCD caused by DENV4 was 70.6% (95% CI 39.9- 85.6) among trial participants who were seropositive at baseline 57 months after the first dose [ClinicalTrials.gov NCT02747927, results forthcoming].

[56] The point estimate for VE against VCD caused by DENV4 among baseline seropositive children was moderately high (70.6%) with a moderately wide confidence interval, so one point would have been added for effect size, but the maximum score is 4.

GRADE TABLE 5b: Efficacy in seropositive children against hospitalized VCD (DENV4).

Population: Baseline seropositive immunocompetent children 4-16 years in endemic countries
Intervention: 2 doses of TAK-003 administered 3 months apart
Comparison: Placebo
Outcome: Hospitalized VCD caused by DENV4

What is the efficacy of 2 doses of TAK-003 in preventing **hospitalized VCD caused by DENV4** compared to placebo in baseline seropositive immunocompetent children 4-16 years of age in endemic countries?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		1 RCT[57] [1]	4
	Factors decreasing confidence	Limitation in study design	Serious[58]	-1
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	Serious[59]	-1
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable[60]	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			2
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **limited level of confidence** that the true effect lies close to the estimate of the effect on the health outcome.

[57] TAK-003 was evaluated in a Phase III safety and efficacy randomised controlled trial (n=20,099 healthy participants ages 4-16 randomised 2:1 to receive two doses of TAK-003 or placebo three months apart) at 26 sites in eight dengue-endemic countries. Overall vaccine efficacy (VE) against hospitalized VCD caused by DENV4 was 100% (NE, NE) in baseline seropositive individuals 57 months after dose one, but there was only one case among baseline seronegative individuals, which was detected among a placebo recipient [ClinicalTrials.gov NCT02747927, results forthcoming].

[58] There were no defined thresholds for hospitalisation (determined by the treating clinician) and heterogeneity in the proportion of cases hospitalized between trial sites. All participants with a positive rapid antigen test for non-structural protein 1 (NS1) in serum were hospitalised for observation at the DEN-301 sites in Sri Lanka (68% hospitalisation rate, or 70 of 103 VCD cases as compared to 72 of 457 VCD cases across other sites), and platelet count and ultrasound examination for plasma leakage were conducted more frequently, leading to a higher proportion of patients being classified as having dengue haemorrhagic fever (DHF).

[59] While the point estimates of VE appear are very (100%; NE, NE) against hospitalized VCD caused by DENV4 among baseline seropositive children, there were too few cases to make any determination around the certainty of evidence on efficacy (3 cases in placebo recipients, 0 in TAK-003 recipients during safety follow-up).

[60] While the point estimate for VE against hospitalized VCD caused by DENV4 in baseline seropositive children appears high (100%), which is a large effect, it is based on three cases over a 57-month period, so no points were added for effect size.

	Conclusion	TAK-003 demonstrated efficacy against hospitalized VCD caused by DENV4 among trial participants 4-16 years of age who were seropositive at baseline.

GRADE TABLE 5c: Efficacy in seronegative children against VCD (DENV4).

Population: Baseline seronegative immunocompetent children 4-16 years in endemic countries
Intervention: 2 doses of TAK-003 administered 3 months apart
Comparison: Placebo
Outcome: VCD caused by DENV 4

What is the efficacy of 2 doses of TAK-003 in preventing **virologically confirmed dengue (VCD) caused by DENV4** compared to placebo **in baseline seronegative** immunocompetent children 4-16 years of age in endemic countries?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		1 RCT[61] [1]	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	Serious[62]	-1
		Imprecision	Very serious[63]	-2
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			1
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **very low level of confidence** that the true effect lies close to the estimate of the effect on the health outcome.

[61] TAK-003 was evaluated in a Phase III safety and efficacy randomised controlled trial (n=20,099 healthy participants ages 4-16 randomised 2:1 to receive two doses of TAK-003 or placebo three months apart) at 26 sites in eight dengue-endemic countries. Estimated vaccine efficacy (VE) of -105.6% (95% CI -628.7- 42.0) against VCD caused by DENV4 among baseline seronegative individuals 57 months after dose one [ClinicalTrials.gov NCT02747927, results forthcoming].
[62] One point was deducted for indirectness given the small number of cases of VCD caused by DENV4 among baseline seronegative participants in DEN-301 (15 total over a 57-month period). There was substantial heterogeneity in the number of cases of DENV4 between sites and the age distribution of these cases.
[63] A negative point estimate of VE (-105.6%) against VCD caused by DENV4 among baseline seronegative individuals 57 months after dose one was observed, with a very wide confidence interval that crosses zero (95% CI -628.7- 42.0). There were only 15 total cases of DENV4 among baseline seronegative individuals over a 57-month period, so there is low confidence in this estimate, but it still suggests that the vaccine is not protective against VCD caused by DENV4.

	Conclusion	Efficacy of TAK-003 against VCD caused by DENV4 cannot be demonstrated among trial participants 4-16 years of age who were seronegative at baseline. Point estimates are negative with wide confidence intervals. A safety risk cannot be ruled out.

GRADE TABLE 5d: Efficacy in seronegative children against hospitalized VCD (DENV4).

Population: Baseline seronegative immunocompetent children 4-16 years in endemic countries
Intervention: 2 doses of TAK-003 administered 3 months apart
Comparison: Placebo
Outcome: Hospitalized VCD caused by DENV 4

What is the efficacy of 2 doses of TAK-003 in preventing **hospitalized VCD caused by DENV4 compared to placebo in baseline seronegative** immunocompetent children 4-16 years of age in endemic countries?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		1 RCT[64] [1]	4
	Factors decreasing confidence	Limitation in study design	Serious[65]	-1
		Inconsistency	None serious	0
		Indirectness	Serious[66]	-1
		Imprecision	Very serious[67]	-2
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			1[68]
Summary of Findings	Statement on the certainty of evidence			Evidence provides a **very low level of confidence** that the true effect lies close to that of the estimate of the effect on the health outcome.

[64] TAK-003 was evaluated in a Phase III safety and efficacy randomised controlled trial (n=20,099 healthy participants ages 4-16 randomised 2:1 to receive two doses of TAK-003 or placebo three months apart) at 26 sites in eight dengue-endemic countries.
[65] There were no defined thresholds for hospitalisation (determined by the treating clinician) and heterogeneity in the proportion of cases hospitalized between trial sites. All participants with a positive rapid antigen test for non-structural protein 1 (NS1) in serum were hospitalised for observation at the DEN-301 sites in Sri Lanka (68% hospitalisation rate, or 70 of 103 VCD cases as compared to 72 of 457 VCD cases across other sites), and platelet count and ultrasound examination for plasma leakage were conducted more frequently, leading to a higher proportion of patients being classified as having dengue haemorrhagic fever (DHF) [ClinicalTrials.gov NCT02747927].
[66] One point was deducted for indirectness given the small number of cases at a few sites of VCD leading to hospitalization caused by DENV4 among baseline seronegative participants in DEN-301 (1 total over 57 months).
[67] There was only one case of hospitalized VCD caused by DENV4 among seronegative subjects, which was in the placebo group, so no determination of efficacy could be made.
[68] While four points were deducted on account of limitations in study design, imprecision, and indirectness, 1 is the lowest possible score.

	Conclusion	The efficacy of TAK-003 against hospitalized VCD could not be demonstrated because of the low number of cases in the trial with wide a very wide uncertainty for the vaccine efficacy estimate. A safety risk cannot be ruled out.

Grade Table 6a: Efficacy in children (any serostatus) against DHF/severe dengue.

Population: Immunocompetent children 4-16 years in endemic countries
Intervention: 2 doses of TAK-003 administered 3 months apart
Comparison: Placebo
Outcome: Dengue haemorrhagic fever (DHF)/Severe Dengue caused by any serotype

What is the efficacy of **DHF/Severe Dengue caused by any serotype compared to placebo** following two doses of TAK-003 in immunocompetent children 4-16 years of age in endemic countries?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		1 RCT[69] [2]	4
	Factors decreasing confidence	Limitation in study design	Serious[70]	-1
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	Very serious[71]	-2
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			1
Summary of Findings	Statement on the certainty of evidence			Evidence provides a **very level of low confidence** that the true effect lies close to that of the estimate of the effect on the health outcome

[69] TAK-003 was evaluated in a Phase III safety and efficacy randomised controlled trial (n=20,099 healthy participants ages 4-16 randomised 2:1 to receive two doses of TAK-003 or placebo three months apart) at 26 sites in eight dengue-endemic countries.

[70] Platelet counts and ultrasound to monitor for plasma leakage were conducted more often at the Sri Lanka sites compared to others.

[71] Estimated vaccine efficacy (VE) against severe dengue 30 days to 18 months following the second dose was 2.3% (95% CI -997.5- 91.1), which is very low with a very wide confidence interval that crosses zero. The estimated VE against DHF 30 days to 18 months after the second dose was 85.9%, which is quite high, but with a wide confidence interval (95% CI 31.9- 97.1), and there were only 9 cases during the Part II follow-up period. At 57 months, estimated vaccine efficacy (VE) against severe dengue was 90.2% (95% CI 16.4- 98.9) among baseline seropositive and –990.0 (NE, NE) among baseline seronegative children. VE against DHF at 57 months was 80.9% (95% CI 46.3- 93.2) among baseline seropositive (78.7% excluding Sri Lanka data) and –3.4% (95% CI -464.7- 81.1) among baseline seronegative children (47.5% excluding Sri Lanka data) [ClinicalTrials.gov NCT02747927, results forthcoming]. There were only 2 cases of severe dengue (both caused by DENV3) and 4 cases of DHF among baseline seronegative children during the safety follow-up period (57 months after dose 1). Given the high level of variability and the wide confidence intervals associated with these estimates, as well as the small numbers overall, two points were deducted.

	Conclusion	Efficacy against severe dengue and DHF caused by any serotype in immunocompetent children 4-16 years of age was not demonstrated. An excess risk of severe dengue and DHF cannot be ruled out.

GRADE TABLE 6b: Efficacy in seropositive children against DHF/severe dengue.

Population: Baseline seropositive immunocompetent children 4-16 years in endemic countries
Intervention: 2 doses of TAK-003 administered 3 months apart
Comparison: Placebo
Outcome: Dengue haemorrhagic fever (DHF)/Severe Dengue caused by any serotype

What is the efficacy of **DHF/Severe Dengue caused by any serotype** compared to placebo **in baseline seropositive** following two doses of TAK-003 in immunocompetent children 4-16 years of age in endemic countries?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		1 RCT[72] [2]	4
	Factors decreasing confidence	Limitation in study design	Serious[73]	-1
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	Serious[74]	-1
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable[75]	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			2
Summary of Findings	Statement on the certainty of evidence			Evidence provides a **limited level of confidence** that the true effect lies close to that of the estimate of the effect on the health outcome.

[72] TAK-003 was evaluated in a Phase III safety and efficacy randomised controlled trial (n=20,099 healthy participants ages 4-16 randomised 2:1 to receive two doses of TAK-003 or placebo three months apart) at 26 sites in eight dengue-endemic countries.
[73] Platelet counts and ultrasound to monitor for plasma leakage were conducted more often at the Sri Lanka sites compared to others.
[74] Estimated vaccine efficacy (VE) against DHF among baseline seropositive participants in DEN-301 at 57 months was 90.2% (95% CI 16.4- 98.9), which is high, but with a wide confidence interval (only six cases of severe dengue among baseline seropositive during this period). VE against DHF was 80.9% (95% CI 46.3- 93.2) or 78,7% (95% CI 17.5- 94.5) excluding Sri Lanka data, but there were only 18 cases of DHF among baseline seropositive (or 10 cases excluding Sri Lanka data) during this period [ClinicalTrials.gov NCT02747927, results forthcoming]. These point estimates are high, but have wide confidence intervals and are based on very small numbers, so one point was deducted.
[75] Even though the point estimate of efficacy was over 80%, no points were added for effect size due to concerns about imprecision.

	Conclusion	Efficacy against severe dengue and DHF caused by any serotype in baseline seropositive immunocompetent children 4-16 years of age was demonstrated, albeit based on a very small number of cases.

Part II. GRADE questions on the efficacy in adults 18 years to 60 years (table 7a)

GRADE TABLE 7a: Efficacy in adults (any serostatus) against VCD (any serotype).

Population: Adults 18-60 years
Intervention: 2 doses of TAK-003 administered 3 months apart
Comparison: Placebo
Outcome: VCD caused by any serotype

What is the efficacy of two doses of TAK-003 compared to placebo against **virologically confirmed dengue caused by any serotype in adults 18-60 yearsr**?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		Multiple RCTs[76][2, 3]	4
	Factors decreasing confidence	Limitation in study design	Serious[77]	-1
		Inconsistency	None serious	0
		Indirectness	Very serious[78]	-2
		Imprecision	None serious	0
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			1
Summary of Findings	Statement on the certainty of evidence			Evidence provides a **very low level of confidence** that the true effect lies close to that of the estimate of the effect on the health outcome.

[76] Data on the immunogenicity of TAK-003 among seronegative adults are available from 12 RCTs conducted in both endemic and non-endemic settings. Four phase 3 trials and one phase 2 trial were conducted in dengue non-endemic areas and generated data on the immunogenicity of TAK-003 in baseline seronegative subjects. Results from all trials showed that TAK-003 induced elevated GMTs of neutralizing antibodies, which remained substantially higher than baseline levels at all timepoints, and seropositivity rates following administration of TAK-003 exceeded 95% in most trials.

[77] Immunobridging was conducted comparing immunogenicity obtained in the large Phase 3 randomized, placebo-controlled efficacy trial (DEN-301) conducted in children and adolescents ages 4-16 years living in dengue-endemic settings in Asia and Latin America with immunogenicity data generated from a Phase 3 lot-to-lot consistency study conducted in adults ages 18-60 years living in non-endemic areas of the United States. While only individuals who were seronegative at baseline in each study were included in the comparative analysis to maximize comparability, this is still not a head-to-head comparison given differences between the study populations, so one point was deducted.

[78] Assumptions about efficacy based on immunobridging would be based on antibody titre levels. Given that there is no good correlate of protection, these immunogenicity data do not provide compelling evidence of vaccine efficacy in this group, so two points were deducted.

	Conclusion	Studies to assess efficacy of TAK-003 against VCD caused by any serotype in adolescents and adults 18 years and older have not yet been conducted. Only immunogenicity results are available. Efficacy is inferred based on a comparison of neutralizing antibody levels elicited in adults and among children in whom efficacy data are available.

Part III. GRADE questions on the safety of the TAK-003 vaccine

GRADE TABLE 8a: Safety in children and adults (any serostatus) with respect to non-dengue severe adverse events.

Population: Immunocompetent children 4-16 years and adults 18-60 years
Intervention: Following either dose of TAK-003
Comparison: Placebo
Outcome: Non-dengue-related severe adverse events (SAEs)

What is the occurrence of **non-dengue-related severe adverse events** following either dose of TAK-003 compared to placebo in immunocompetent children 4-16 years and adults 18-60 years of age?				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		1 RCT[79] [2]	4
	Factors decreasing confidence	Limitation in study design	None serious	0
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	Serious[80]	-1
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable[81]	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of the certainty of the evidence			3
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **moderate level of confidence** that the true effect lies close to the estimate of the effect on the health outcome.

[79] TAK-003 was evaluated in a Phase III safety and efficacy randomised controlled trial (n=20,099 healthy participants ages 4-16 randomised 2:1 to receive two doses of TAK-003 or placebo three months apart) at 26 sites in eight dengue-endemic countries. Solicited adverse events occurred more frequently in the vaccine arm whereas there was similar reporting of unsolicited events between the vaccine and control arms. The most frequent TAK-003 vaccine-related unsolicited adverse events were injection site pruritis (0.7%), bruising (0.6%) and pyrexia (0.2%). Overall, the vaccine was well tolerated.
Cumulative rates of serious adverse events were similar between groups 30 days to 18 months after dose 2 (4.0% in vaccine group and 4.8% in placebo group). There was one SAE considered related to TAK-003 compared to 5 related SAEs in 4 placebo recipients 57 months after first dose. Death occurred in 16 subjects in the vaccine group (0.09%) and 9 (0.11%) in the placebo group. None were considered causally related and there were no fatal cases of dengue reported.
[80] One point deducted for imprecision as sample size was not adequately large to detect rare SAEs.
[81] Given the size of the study, there can be a high degree of confidence that there is not an increased safety signal associated with non-dengue severe adverse events; however, no points were added as 4 is the maximum score.

	Conclusion	There is no observed safety signal (non-dengue severe adverse events) associated with TAK-003 among immunocompetent trial participants 4-16 years of age.

GRADE TABLE 8b: Safety in seronegative children in relation to DHF/severe dengue.

Population: Baseline seronegative immunocompetent children 4-16 years
Intervention: 2 doses of TAK-003 administered 3 months apart
Comparison: Placebo
Outcome: Dengue haemorrhagic fever (DHF)/Severe Dengue caused by any serotype

What is the efficacy of **DHF/Severe Dengue caused by any serotype** compared to placebo **in baseline seronegative** following two doses of TAK-003 in immunocompetent children 4-16 years of age?[82]				
			Rating	Adjustment to rating
Certainty	No. of studies/starting rating		1 RCT[83] [1]	4
	Factors decreasing confidence	Limitation in study design	Serious[84]	-1
		Inconsistency	None serious	0
		Indirectness	None serious	0
		Imprecision	Very serious[85]	-2
		Publication bias	None serious	0
	Factors increasing confidence	Large effect	Not applicable	0
		Dose-response	Not applicable	0
		Antagonistic bias and confounding	Not applicable	0
	Final numerical rating of certainty of the evidence			1
Summary of Findings	Statement on the certainty of evidence			Evidence supports a **very low level of confidence** that the true effect lies close to the estimate of the effect on the health outcome.

[82] GRADE table evaluating the certainty of evidence of the efficacy of TAK-003 against DHF and severe dengue was included in the Safety tables, as this table evaluates risk associated with an increase in DHF following immunization, while tables evaluating vaccine efficacy in all subjects and baseline seropositive subjects (Part I tables) represent benefits.
[83] TAK-003 was evaluated in a Phase III safety and efficacy randomised controlled trial (n=20,099 healthy participants ages 4-16 randomised 2:1 to receive two doses of TAK-003 or placebo three months apart) at 26 sites in eight dengue-endemic countries.
[84] Platelet counts and ultrasound to monitor for plasma leakage were conducted more often at the Sri Lanka sites compared to others.
[85] There were very few cases of severe dengue and/or DHF in the trial. A small excess of severe dengue and DHF cases were observed in baseline seronegative vaccinees 57 months after dose one (2 cases of severe dengue in baseline seronegative TAK-003 recipients vs 0 in seronegative placebo recipients; 4 cases of DHF in baseline seronegative TAK-003 recipients vs 2 in seronegative placebo recipients), but the numbers were too small to draw inferences, particularly because trial participants were randomized 2:1 to receive TAK-003 or placebo. All severe cases among seronegative vaccine recipients were caused by DENV3 ClinicalTrials.gov NCT02747927, results forthcoming].

	Conclusion	TAK-003 is not associated with a statistically significant increased risk of severe dengue or DHF among immunocompetent children ages 4-16 who were seronegative at baseline. A risk of excess cases of severe dengue or DHF cannot be ruled out with the available data.

References

1. clinicaltrials.gov. *Efficacy, Safety and Immunogenicity of Takeda's Tetravalent Dengue Vaccine (TDV) in Healthy Children (TIDES)*. 2022; Available from: https://clinicaltrials.gov/ct2/show/NCT02747927.
2. European Medicines Agency, *Assessment report Qdenga.* 2022.
3. LeFevre, I., et al., *Bridging the immunogenicity of a tetravalent dengue vaccine (TAK-003) from children and adolescents to adults.* npj Vaccines, 2023. **8**(1): p. 75.