

Work Group Summary and Interpretation of TAK-003 Efficacy, Safety, and Immunogenicity Data

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Phase 3 Study (DEN-301)

- **Design:** double-blind, placebo-controlled study
 - Randomized to TAK-003 or placebo in a 2:1 ratio
- **Ages:** children 4–16 years
- **Sites:** conducted across 5 countries in Latin America and 3 countries in Asia
- **Duration:** ~57 months after first dose

DEN-301 population and outcomes evaluated

- Safety set included 20,071 participants.
 - 28% of participants were seronegative at baseline.
- Primary endpoint was virologically-confirmed dengue (VCD) from any serotype one year after the second dose.*
- Secondary endpoints, stratified by serotype and serostatus, included:
 - VCD
 - Hospitalization for dengue
 - Dengue hemorrhagic fever (1997 WHO definition)
 - Trial-specific severe dengue definition

*Exploratory endpoints were analyzed using the per protocol set (19,021 participants; 28% seronegative). Biswal, Lancet 2020.

All VE data shown in the following summary are for:

~57 months follow-up

and

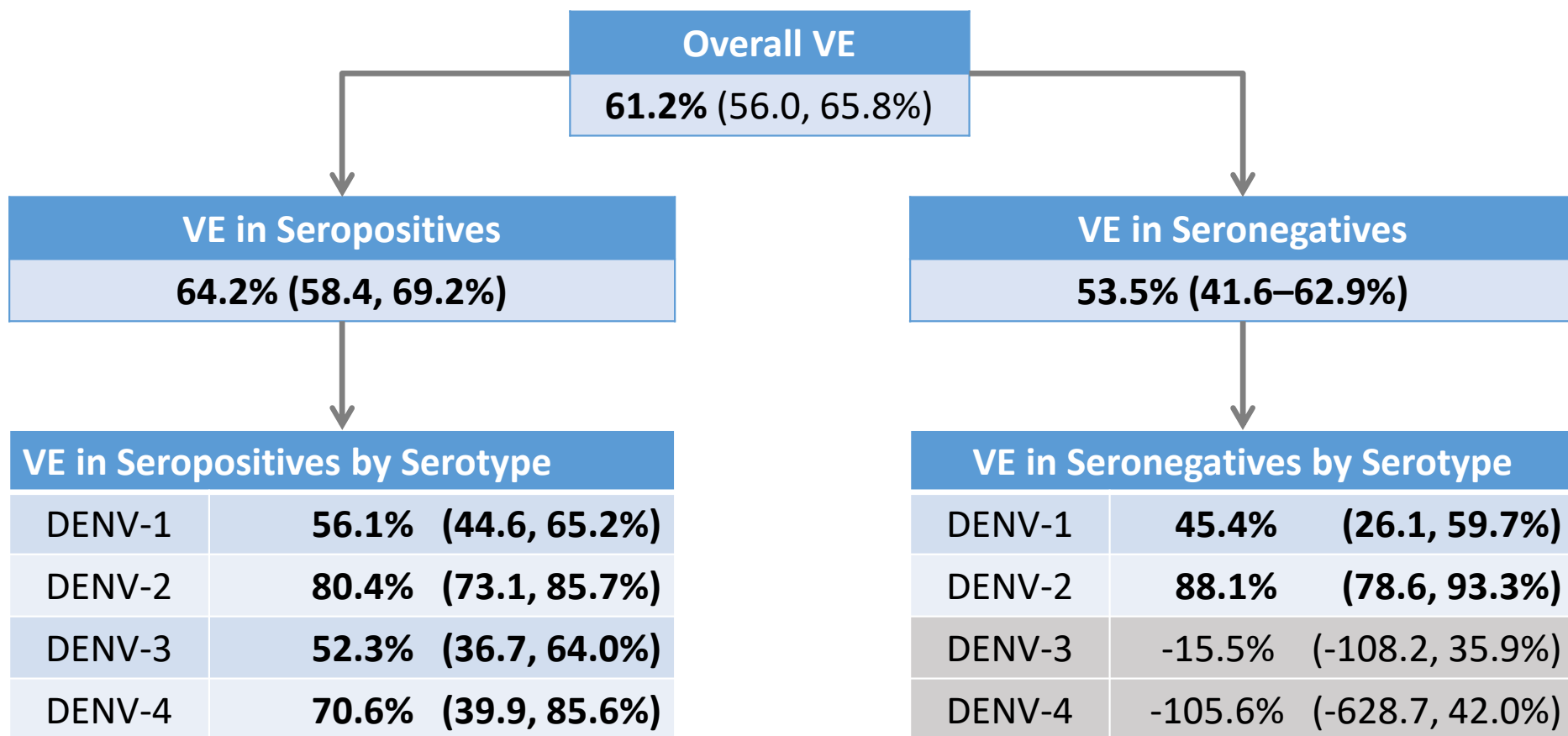
include all RCT trial sites*

*Participants included from the safety set.

VE for VCD

Vaccine Efficacy*

Outcome: **Virologically Confirmed Dengue**



*57 months after first dose, significant results **bolded**. Number for seropositive placebo participants 4,855 and vaccine 9,666; Seronegative placebo 1,832 and vaccine 3,714.

Summary: Virologically Confirmed Dengue

- **Seropositives**

- Protection against all 4 serotypes.

- **Seronegatives**

- Protection against DENV-1 and -2.
- No efficacy for DENV-3 and -4.
 - Data insufficient to rule out an increased risk of VCD among vaccinees.

VE for hospitalization

Vaccine Efficacy*

Outcome: Hospitalization

Overall VE

84.1% (77.8, 88.6%)

VE in Seropositives

85.9% (78.7, 90.7%)

VE in Seropositives by Serotype

DENV-1	66.8% (37.4, 82.3%)
DENV-2	95.8% (89.6, 98.3%)
DENV-3	74.0% (38.6, 89.0%)
DENV-4	100% (NE, NE)[†]

[†]DENV-4 Placebo events: 3 TAK-003 events: 0

VE in Seronegatives

79.3% (63.5, 88.2%)

VE in Seronegatives by Serotype

DENV-1	78.4%	(43.9, 91.7%)
DENV-2	100%	(NE, NE)[§]
DENV-3	-87.9%	(-573.4, 47.6%) [¶]
DENV-4	100%	(NE, NE) ^{**}

[§]DENV-2 Placebo events: 23 TAK-003 events: 0
[¶]DENV-3 Placebo events: 3 TAK-003 events: 11
^{**}DENV-4 Placebo events: 1 TAK-003 events: 0

*57 months after first dose, significant results **bolded**. Number for seropositive placebo participants 4,855 and vaccine 9,666; Seronegative placebo 1,832 and vaccine 3,714.

Hospitalization for DENV-3 and DENV-4 among seronegative children was low

	Placebo n=1832	Incidence density/100 person-years	TAK-003 n=3714	Incidence density/100 person-years	VE (95% CI)
DENV-1	14	0.17	6	0.03	78.4% (43.9, 91.7%)
DENV-2	23	0.28	0	0.0	100% (NE, NE)
DENV-3	3	0.04	11	0.07	-87.9% (-573.4, 47.6%)
DENV-4	1	0.01	0	0.0	100% (NE, NE)

Summary: Hospitalizations

- **Seropositives**

- Protection against all 4 serotypes.
- Few hospitalizations for DENV-4.

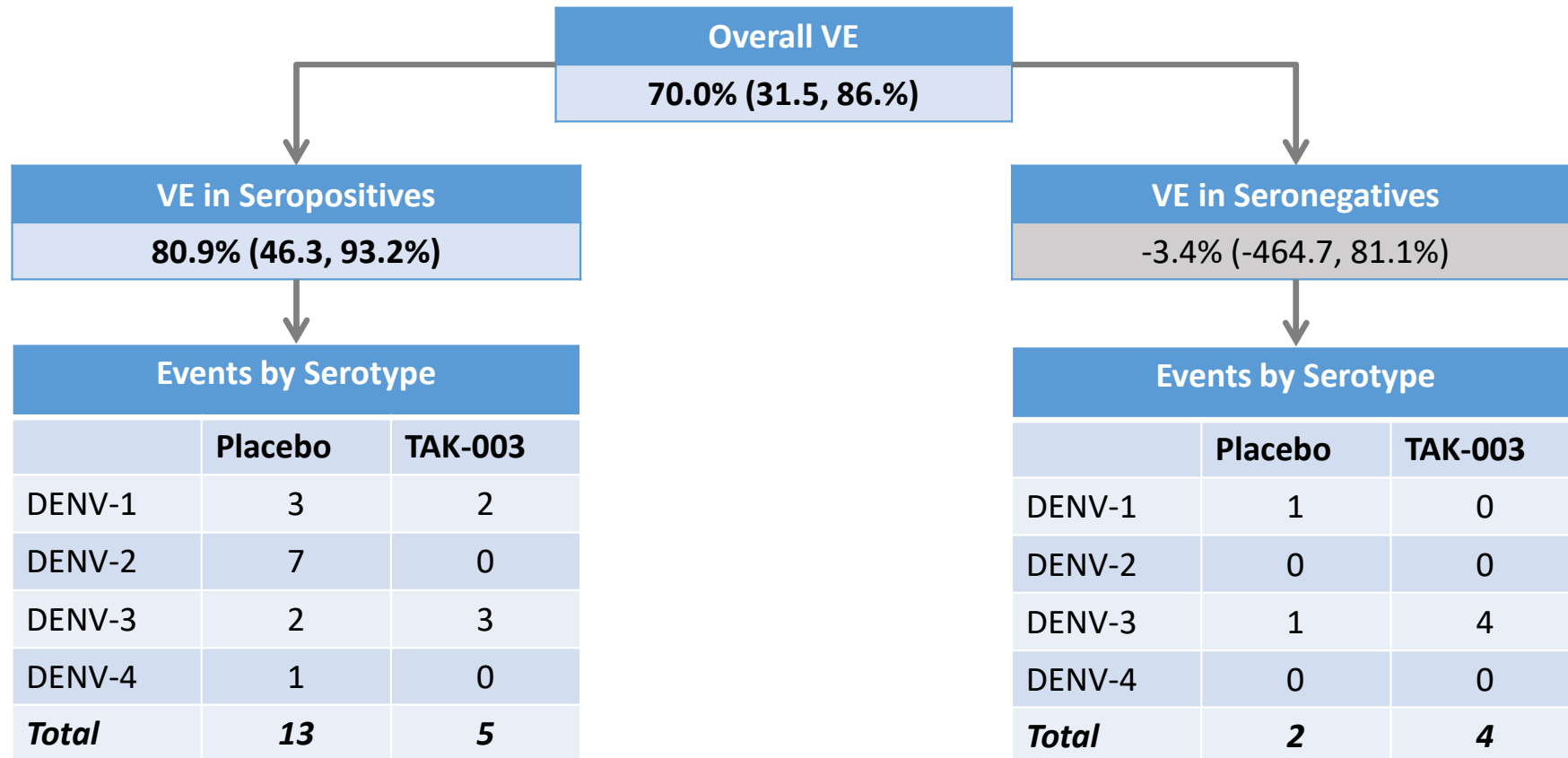
- **Seronegatives**

- Protection against DENV-1, and -2.
 - One hospitalization due to DENV-4.
- No efficacy for DENV-3
 - Data insufficient to rule out an increased risk of hospitalization among vaccinated children with DENV-3.

VE for Severe Dengue

Vaccine Efficacy*

Outcome: Dengue Hemorrhagic Fever (1997 Definition)

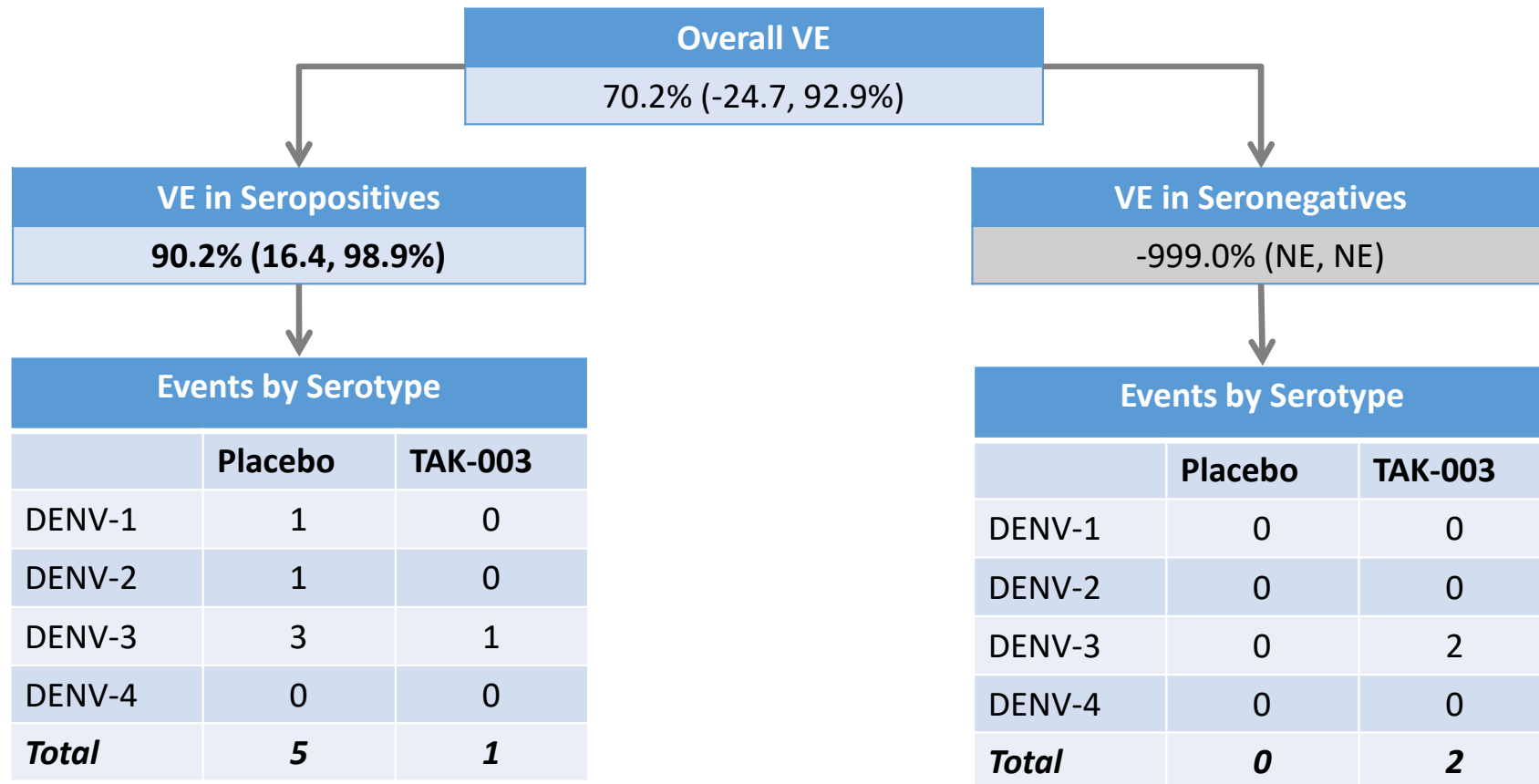


*57 months after first dose, significant results for vaccine efficacy **bolded**. Number for seropositive placebo participants 4,855 and vaccine 9,666; Seronegative placebo 1,832 and vaccine 3,714.

VE by serostatus from unpublished data from Takeda.

Vaccine Efficacy*

Outcome: **Severe Dengue**
Trial-specific Definition



*57 months after first dose, significant results for vaccine efficacy **bolded**. Number for seropositive placebo participants 4,855 and vaccine 9,666; Seronegative placebo 1,832 and vaccine 3,714.

VE by serostatus from unpublished data from Takeda.

Summary: Severe Dengue

- **Small number of events, difficult to stratify by serotype.**
- **Seropositives:**
 - Offered protection against dengue hemorrhagic fever and trial-specific definition of severe dengue due to any serotype.
- **Seronegatives:**
 - Few events.
 - No efficacy for dengue hemorrhagic fever and trial-specific definition of severe dengue due to any serotype.

Immunogenicity and Safety

Immunogenicity

- Subset of 2,518 TAK-003 and 1,247 placebo recipients (28% seronegative in each arm)
- GMTs highest for DENV-2 serotype among TAK-003 recipients.
 - GMTs remained stable until 51 months after 1st dose for DENV-1, -3, and -4.
 - GMTs for DENV-2 decreased over time but remained higher than other serotypes at 51 months after 1st dose.

Vaccine safety

- **Solicited AEs were higher among recipients of TAK-003** compared to placebo.*
 - Local: TAK-003 43%; placebo 26%
 - General: TAK-003 46%; placebo 40%
- **Unsolicited AEs were similar** between recipients of TAK-003 and placebo.*
 - Common TAK-003 unsolicited AEs:
 - injection site pruritus (0.7%)
 - bruising (0.6%)
 - pyrexia (0.2%)

*Adverse events were analyzed using the safety set.

Vaccine safety: serious adverse events (SAE)

- **SAEs were similar** among recipients of TAK-003 (8%) and placebo (10%).
 - 1 TAK-003 and 4 placebo recipients had SAEs related to the intervention
- **Common SAEs (>0.2%)** among recipients included:
 - **Dengue fever** (TAK-003: 0.5%; placebo: 2%).
 - **Dengue hemorrhagic fever** (TAK-003: 0.1%; placebo 0.5%).
- Incidence of death was 0.1% in both TAK-003 (n=16) and placebo (n=9) recipients.
 - **No deaths attributed to TAK-003.**

Summary

Findings for TAK-003

- **Protects seropositive** recipients against VCD and hospitalization due to **any serotype**.
- **Protects seronegative** recipients against VCD and hospitalization for **DENV-1 or DENV-2**.
- Does **NOT protect seronegative** recipients against VCD and hospitalization for **DENV-3**.
- **DENV-4** assessment among seronegative children is limited by low number of events.
 - No protection against VCD for DENV-4.
 - Only one DENV-4 hospitalization limits efficacy assessment.
- Unsolicited, serious adverse events, and deaths similar in vaccine and placebo arms.

Summary

Pending Questions/Observations

- Vaccine efficacy against hospitalizations for **DENV-4 among seronegative** recipients is unknown.
- **No efficacy against hospitalizations for DENV-3 among seronegative** vaccine recipients compared to placebo (-87.9%; 95% CI: -573.4–47.6%).
 - Data insufficient to rule out an increased risk among vaccine recipients.
- Unclear significance of immunogenicity data because no clearly defined correlate of immune protection exists.

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