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

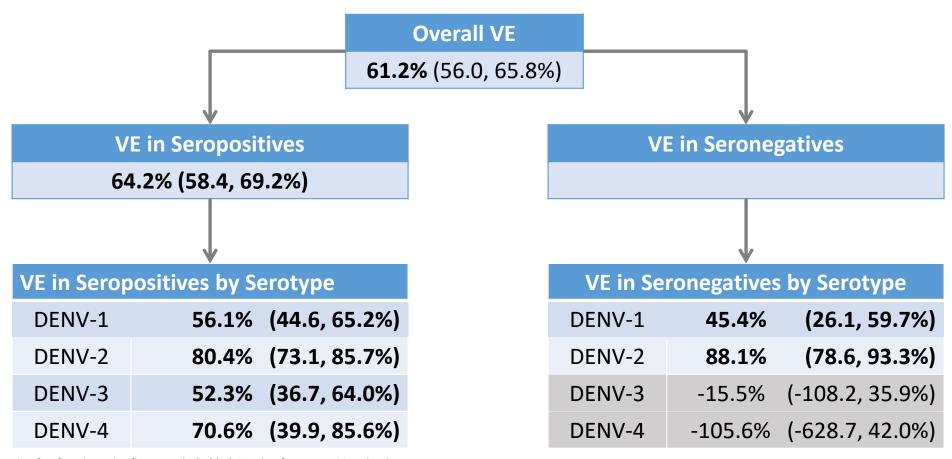
include all RCT trial sites*

^{*}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.

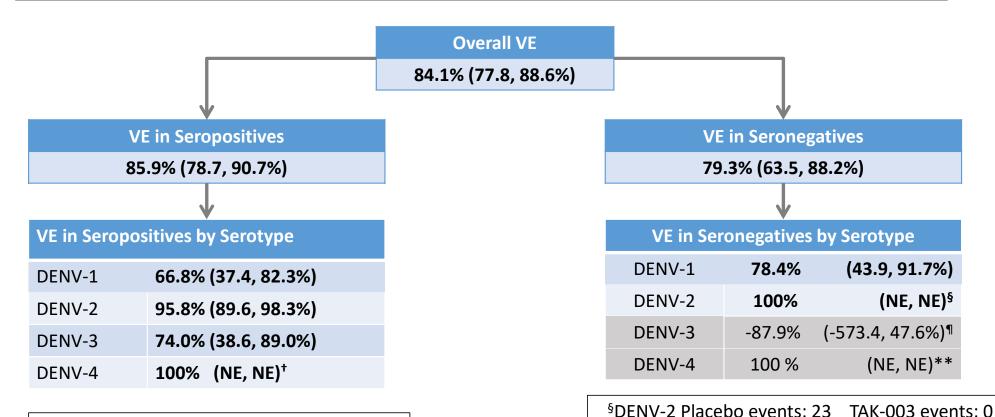
Seronegatives

- 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



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

**DENV-4 Placebo events: 1 TAK-003 events: 0

¶DENV-3 Placebo events: 3

TAK-003 events: 11

^{*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.

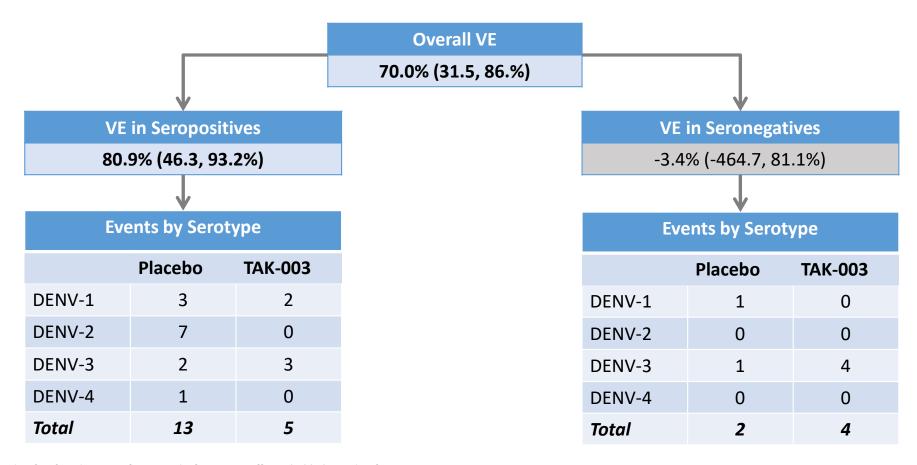
Seronegatives

- 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



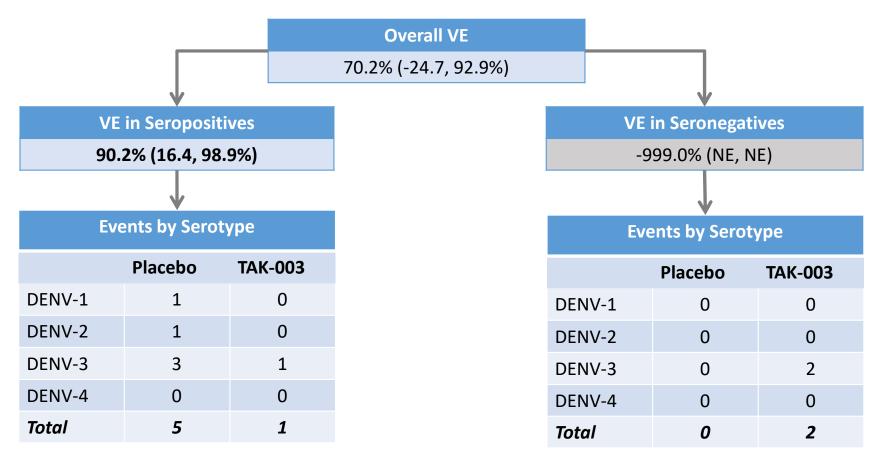
Outcome: Dengue Hemorrhagic Fever (1997 Definition)



^{*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.

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.

Summary: Severe Dengue

Small number of events, difficult to stratify by serotype.

Seropositives:

• Offered protection against dengue hemorrhagic fever and trialspecific 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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