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**

Overall VE

61.2% (56.0, 65.8%)

VE in Seropositives

64.2% (58.4, 69.2%)

VE in Seronegatives

VE in Seropositives by Serotype

DENV-1	**56.1%**	**(44.6, 65.2%)**
DENV-2	**80.4%**	**(73.1, 85.7%)**
DENV-3	**52.3%**	**(36.7, 64.0%)**
DENV-4	**70.6%**	**(39.9, 85.6%)**

VE in Seronegatives by Serotype

DENV-1	**45.4%**	**(26.1, 59.7%)**
DENV-2	**88.1%**	**(78.6, 93.3%)**
DENV-3	-15.5%	(-108.2, 35.9%)
DENV-4	-105.6%	(-628.7, 42.0%)

*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.

Unpublished data presented by Takeda to ACIP WG

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.

Unpublished data presented by Takeda to ACIP WG

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)**

Overall VE

70.0% (31.5, 86.%)

VE in Seropositives

80.9% (46.3, 93.2%)

Events by Serotype

	Placebo	TAK-003
DENV-1	3	2
DENV-2	7	0
DENV-3	2	3
DENV-4	1	0
Total	***13***	***5***

VE in Seronegatives

-3.4% (-464.7, 81.1%)

Events by Serotype

	Placebo	TAK-003
DENV-1	1	0
DENV-2	0	0
DENV-3	1	4
DENV-4	0	0
Total	***2***	***4***

*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**

Overall VE

70.2% (-24.7, 92.9%)

VE in Seropositives

90.2% (16.4, 98.9%)

Events by Serotype

	Placebo	TAK-003
DENV-1	1	0
DENV-2	1	0
DENV-3	3	1
DENV-4	0	0
Total	***5***	***1***

VE in Seronegatives

-999.0% (NE, NE)

Events by Serotype

	Placebo	TAK-003
DENV-1	0	0
DENV-2	0	0
DENV-3	0	2
DENV-4	0	0
Total	***0***	***2***

*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.

Geometric mean titers (GMTs) calculated using $PRNT_{50}$
Seropositivity = reciprocal neutralizing titers ≥10

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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