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

Gabriela Paz-Bailey, MD, PhD, MSc

Dengue Branch Chief

Division of Vector Borne Diseases, NCEZID, CDC

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

53.5% (41.6–62.9%)

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Unpublished data presented by Takeda to ACIP WG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.

ACIP Dengue Vaccines Workgroup

ACIP Members

Wilbur Chen (Chair)

Kathy Poehling

Beth Bell

Veronica McNally

CDC Co-Lead

Gabriela Paz-Bailey

Laura Adams

Ex Officio Members

Kaitlyn Morabito (NIH)

Ralph LeBlanc (FDA)

Ihid Carneiro Leao (FDA)

Kirk Prutzman (FDA)

Srihari Seshadri (DOD)

Liaison Representatives

Elizabeth Barnett (AAP)

Rob Schechter (AIM)

Consultants

Edwin Asturias

Robert Atmar

Alan Barrett

Iris Cardona

Anna Durbin

Tony Marfin

Kristen Pierce

Anita Shet

CDC Contributors

Josh Wong

Mimi Eckert

Rachel Eidex

Alfonso Hernandez

Susan Hills

Terri Hyde

Mike McNeil

Jorge Munoz

Erin Staples

Cindy Weinbaum

Rita Helfand