# Target Product Profile & Clinical Development Plan

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# TPP/Data of 3 Live attenuated Dengue vaccines (Licensed or in Ph3)

| | CYD-TDV (Dengvaxia) | TAK003 (Qdenga) | TV003 in Ph3 (NIH/Butantan) |
|---|---|---|---|
| Indication | protection from dengue disease, all 4 strains | | |
| Target pop | 6-45 years | 4+ years | 2-59 years |
| Efficacy | | 75% efficacy vs infection among all DEN serotypes and higher for disease<br>12 months after 2nd dose; vs. VCD fever* 80.2%<br>18 months: vs. VCD fever 76.1% (sero+), 66.2% (sero-),<br>vs. Hospitalization 90.4%.<br>54 months; vs VCD fever 61.2% (56.0, 65.8), vs.hospitalization;84.1(77.8,88.6)<br>No efficacy for DENV3 for Naïve subjects, too few cases to conclude DENV4 | 80% protection against any symptomatic dengue disease after a single dose<br>Ph3, 2 yr f/u<br>DENV-1: 89.5% (95% CI, 78.7 to 95.0)<br>DENV-2: 69.6% (95% CI, 50.8 to 81.5) |
| Safety/reactogenicity | | similar safety / tolerability with other similar vaccines | |
| Dose regimen | 3 doses with 6 mo interval | 2 doses, >=8 weeks apart<br>(license: 3 mo interval) | Single dose |
| Durability of protection | | at least 4 years | |
| Route | SC | SC | SC |
| Stability/Storage | 3 years 2- 8°C | 18 month at 2°C - 8°C | Stable at 2 to 8°C |
| Presentation | lyophilized | lyophilized, mono & multi-dose | lyophilized, 10 d vial |
| PMS | | ADE monitoring, protection of the target population, indirect effects (herd immun ity), potential serotype replacement to be monitored. | |

*VCD fever: A virologically-confirmed dengue case is defined as febrile illness (defined as temperature ≥38°C on any 2 of 3 consecutive days) or illness clinically suspected to be dengue by the Investigator with a positive serotype-specific RT-PCR.

# Target Product Profile of mRNA Dengue Vaccine

| | Preferred | Critical or Minimal |
|---|---|---|
| Indication | protection from dengue infection, all 4 strains | protection from dengue disease, all 4 strains |
| Target Pop | 2+ | 4-59 years (Peak incidence 5~14 yo) |
| Contraindication | Serious allergic reaction to mRNA vaccine components. | |
| Efficacy | 80% vs. Virologically Confirmed Dengue case*,<br>90% vs. severe disease (hospitalization) against all 4 serotypes | 70% vs. Virologically Confirmed Dengue case*,<br>80% vs. severe disease (hospitalization) against all 4 serotypes |
| Safety/ Reactogenecity | Mild, transient AEs, No serious AEs.<br>No ADE | Safety and reactogenicity profile whereby vaccine benefits outweigh safety risks. No ADE |
| Dose regimen | Single dose | 2 doses |
| Durability | Lifelong | 5 years |
| Route | IM, MAP (if applicable) | IM |
| Stability/Storage | Multiple years at -25~ -15°C<br>When thawed, >6 months at 2 to 8°C | 1 year at -25~ -15°C. When thawed >3 months at 2 to 8°C<br>Pfizer COVID BA.4-5; 2yrs at ULT (-90~-60°C), 10 wks at 2 to 8°C<br>Moderna COVID: 9 months at -25~ -15°C, 30 days at 2 to 8°C |
| Presentation | Lyophilized or Liquid, Single and multi-dose vial,<br>MAP if applicable | Liquid, Multi-dose vial |
| PMS | ADE monitoring, protection of the target population, indirect effects (herd immunity),<br>potential serotype replacement to be monitored. | |

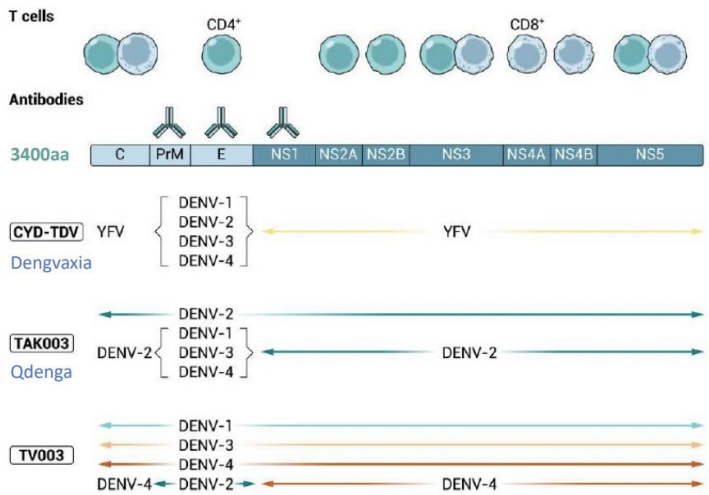


* Case definition: A virologically-confirmed dengue case is defined as febrile illness (defined as temperature ≥38°C on any 2 of 3 consecutive days) or illness clinically suspected to be dengue by the Investigator with a positive serotype-specific RT-PCR.

# T cell immunity is important to provide optimal protection

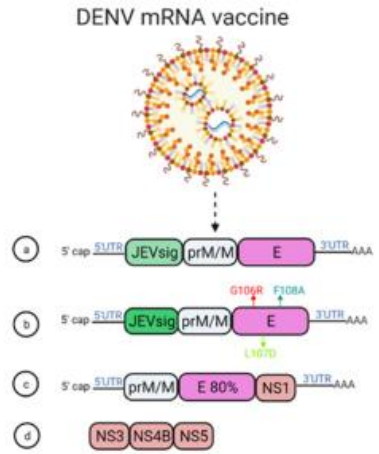
**mRNA construct encoding only Structural protein (PrM and E) might not provide Cellular immunity (CD8+).**

- Majority of CD8+ T cell epitopes are found on NS proteins
  - Dengvaxia induced strong CD8+ T cell response against YF17D-NS3, but muted cross-reactive CD8+ T cell responses against DENV NS3
    *Guy et al, Vaccine 2008*
  - TAK003 and TV003 showed T cell responses to conserved epitopes on NS proteins.
    *Tricou et al, Vaccine 2022.* *Weiskopf et al, J Virol 2015*




*Ooi et al. Sci Transl Med 2023*

- mRNA DENV vaccine Candidates
  - DENV1-NS (NS3, NS4B, NS5) induced a strong CD8+ T cell immune response and conferred significant protection after challenge with DENV1 Roth et al, *Front Immunol* 2019
  - DENV mRNA vaccine based on two structural proteins—prME and E80 and one **non-structural protein** (NS1) from DENV2 elicited strongest neutralizing antibody response against DENV2 and antigen-specific T cell responses
    *Zhang et al, Mol Ther Mothods Clin Dec 2020*




*Mourosi et al. Vaccines 2022*

# Regulatory Pathway Assumption

- **Will depend upon the country of the Manufacturer**
  - Local licensure (ML3/Functional NRA) followed by WHO PQ

- **First licensure should target high-burden populations only**
  - 4-59 years, irrespective of serostatus
  - The rest of the population (below 4 years & above 59 years) could be targeted post-licensure studies/ label extension studies

- **As not established CoP available, clinical endpoint (efficacy) is desirable**
  - Possible only in countries with documented high burden for age-targeted( e.g., many south-east Asian & Latin American countries)

# Regulatory Pathway Assumption

- **Immunology**
  - There is no established immunological correlate of protection against any DENV serotype.
  - **Neutralizing antibody** against each DENV serotype is likely to be the best surrogate marker for efficacy.
  - DENV serotype-specific neutralizing antibody titres should follow WHO guidelines for the plaque-reduction neutralization test (PRNT) (Essential)
  - If alternative methods for determining neutralizing antibody (e.g. high throughput **micro-neutralization assays**) are developed, these should be validated against the PRNT
  - The assay of DENV-specific antibody other than neutralizing antibody (e.g. IgM and IgG ELISA) may be of interest but is not considered to be essential for the assessment of potential vaccine efficacy.
  - It is considered unlikely that data on cell-mediated immunity will provide an immunological correlate of protection.
    - Cell-mediated immunity assays may be useful for the assessment of immunological memory and durability of protection.

Guidelines on the quality, safety and efficacy of dengue tetravalent vaccines (live, attenuated), Annex 2, TRS No 979, Replacement of Annex 1 of WHO Technical Report Series, No. 932

| DENV vaccine | Developer | Platform | Neutralization assay |
|---|---|---|---|
| CYD-TDV | Sanofi Pasteur | Live-attenuated | PRNT (immuno- staining) |
| TAK-003 | Takeda | Live-attenuated | Microneutralization |
| TV003 | NIH/Butantan | Live-attenuated | PRNT (immuno- staining) |

- **Efficacy endpoint**
  - Vaccine Efficacy (VE) of Two Doses of mRNA DENV in Preventing Virologically-Confirmed(RT-PCR) Dengue Fever Induced by Any Dengue Serotype

# Clinical Development Plan

| Phase | Design | Target Population | Target Country | Tentative Sample Size |
|---|---|---|---|---|
| I | Safety, Immunogenicity & Dose escalation/exploration, | Healthy participants aged 18-59 years (seronegative) in non endemic/low endemic country | Non/low endemic country | 80 (TBC) |
| II | Age de-escalation, Safety & Immunogenicity | Adult (18-59 yr), Adolescents (12-17yr), children (4-11yr) in an endemic country | Endemic countries (e.g., Bangladesh) | 180 (TBC) |
| IIb | RCT, Efficacy & Safety trial, mRNA DENV vs Placebo | Healthy participants aged 4 to 11 years in Endemic countries Assumptions: 80% power, 2:1 vaccine to placebo, alpha = 2.5% one-sided, 20% loss-to-follow-up, Incidence: X%, VE=80%, LB>0% | Bangladesh, Nepal, Philippines, Vietnam (Incidence to be confirmed) | Approx. XYZ with 1 yr follow-up Approx.. XYZ with 3 years follow-up |
| III | RCT, Efficacy & Safety + L2L mRNA DENV vs Placebo | Healthy participants aged 4 to 59 years in Endemic countries Assumptions: 90% power, 2:1 vaccine to placebo, alpha = 2.5% one-sided, 20% loss-to-follow-up, Incidence: 1.5%, VE=80%, Superiority margin=30% | Bangladesh, Nepal Philippines, Vietnam Brazil, Colombia, Dominican Republic, Nicaragua, Panama, (Incidence to be confirmed) | Approx. XYZ with 1 yr follow-up Approx.. XYZ with 3 years follow-up |
| IV | Immune Non-Interference with EPI vaccine (Co-ad) | Healthy participants aged 2-11 (or younger) & >50 yr in an Endemic country | | 500(TBC) |
| | Note: All numbers are placeholders only, will be confirmed statistically as per required power for stage and incidence rate for phase IIb/III. | | | |



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