



## Questions and Answers on Dengue Vaccines: Phase IIb study of CYD-TDV

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### **What is the current status of dengue vaccine development?**

No licensed dengue vaccine is currently available. However, there is a significant and continually growing public health need for effective interventions against dengue.<sup>1</sup> A safe, effective and affordable dengue vaccine would represent a major advance for the control of the disease. Several vaccine candidates are currently at different stages of preclinical or clinical development.<sup>2</sup> The candidate currently at the most advanced clinical development stage is a live attenuated tetravalent dengue vaccine developed by Sanofi Pasteur (CYD-TDV), which is under evaluation in phase II and phase III clinical studies.

### **What are the main objectives of the phase IIb study of CYD-TDV in Thailand?<sup>3</sup>**

The primary objective of the phase IIb study is to assess the efficacy of CYD-TDV in preventing dengue disease, after completion of the vaccination schedule of three doses given 6 months apart. Additional objectives include the evaluation of vaccine safety and immunogenicity. The study population consists of 4,002 children aged 4 to 11 years in Ratchaburi Province, Thailand. Efficacy, safety and immunogenicity results, as available one year after completion of the vaccination schedule, are described in a recent publication.<sup>3</sup> The study protocol includes a follow-up period of two additional years, which is currently ongoing.

### **What conclusions can be drawn from the results of the phase IIb study?**

This is the first study conducted to evaluate the efficacy of any dengue vaccine candidate against clinical dengue disease in a population naturally exposed to dengue, which represents a significant advance for the field of dengue vaccine research. The results are therefore of considerable interest to the vaccine research community.

Phase IIb studies are generally designed to provide initial proof-of-concept data, to be corroborated in larger phase III studies. Interpretation of phase IIb study results should therefore be undertaken with caution.

The primary efficacy analysis, as defined in the protocol for this study, is based on the number of dengue cases in vaccinated and control subjects, during a one year observation period following completion of the vaccination schedule. The reported vaccine efficacy result of 30.2% (95% confidence interval: -13.4% to 56.6%) is not statistically significant, and the vaccine efficacy therefore remains inconclusive.

Additional analyses were carried out to explore efficacy after at least one vaccine dose, and against individual dengue virus serotypes. Statistically significant efficacy estimates were reported for three of the four dengue virus serotypes after at least one vaccine dose, but not after three doses. These exploratory analyses, which are based on relatively small numbers of dengue cases, must be interpreted cautiously.

According to a WHO advisory group of experts<sup>4</sup>, the recently published data from this phase IIb study do not yet prove nor disprove efficacy of CYD-TDV against disease caused by any of the four dengue virus serotypes. Further studies in larger populations and different epidemiological settings are needed to assess conclusively the efficacy of this vaccine candidate.



Based on the recently published data, the safety profile of CYD-TDV is satisfactory, for an observation period of 25 months after the first vaccine dose. Continued follow-up of participants in this and other studies will be critical to generate data towards an assessment of long-term safety of CYD-TDV.

Antibody responses to each of the four dengue virus strains in the vaccine were observed in vaccinated subjects. Evaluation of antibody persistence over time will require continued follow-up of participants in this and other studies. Detailed data on the relationship between antibody responses and protection against clinical dengue disease in this study, such as comparisons of antibody levels in vaccinated subjects who developed dengue versus those who did not, remain to be published. Other efficacy studies in different epidemiological settings should also contribute to addressing this critical question.

### **What are the implications for phase III studies and potential future licensure?**

The recently published data from a phase IIb study support the continued evaluation of this vaccine candidate in phase III studies. Phase III efficacy studies of CYD-TDV are currently underway in 31,000 children and adolescents in 10 countries in Asia and Latin America. These large-scale, multi-centre studies in a variety of epidemiological settings will be important to obtain pivotal efficacy results, additional safety data, and further insight into the relationship between vaccine-induced immune responses and protection against clinical dengue disease.

Future licensure of any dengue vaccine candidate will depend on the assessment of quality, safety and efficacy data by national regulatory agencies. Based on currently available evidence, WHO believes that the public health value of CYD-TDV remains to be demonstrated, and further studies are therefore needed.

### **How is WHO involved in dengue vaccine research efforts?**

The role of WHO is to advise and guide the dengue vaccine development activities of the global research community. This includes scientific consensus-building, guidance on vaccine evaluation, and assessment of the evidence base for policy recommendations on vaccine introduction and use. WHO also provides guidance to national regulatory agencies on approaches and methodologies related to the assessment and licensure of vaccines and post-licensure surveillance. In addition, WHO prequalification is a mechanism to ensure that a vaccine meets international standards for quality, safety and efficacy and is appropriate for the target population. Only WHO prequalified vaccines can be supplied to countries through UN agencies.

More information on dengue vaccine development and related WHO activities is available at [http://www.who.int/vaccine\\_research/diseases/dengue/dengue\\_vaccines/en/index.html](http://www.who.int/vaccine_research/diseases/dengue/dengue_vaccines/en/index.html).

### **References**

<sup>1</sup> World Health Organization (2012). Fact sheet: Dengue and severe dengue. Accessible online at <http://www.who.int/mediacentre/factsheets/fs117/en/index.html>

<sup>2</sup> Special Issue (2011): The Development of Dengue Vaccines. *Vaccine*, Volume 29, Issue 42, Pages 7219-7284.

<sup>3</sup> Sabchareon A. et al. (2012). Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai schoolchildren: a randomised, controlled phase 2b trial. *The Lancet* (Published online September 11).

<sup>4</sup> WHO Technical Advisory Group on Dengue Vaccines in Late Stage Development. Further information at [http://www.who.int/vaccine\\_research/committees/dengue\\_tag/en/index.html](http://www.who.int/vaccine_research/committees/dengue_tag/en/index.html)