Vaccine 36 (2018) 3411–3417

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

WHO Report

Clinical development and regulatory points for consideration for second-generation live attenuated dengue vaccines

Kirsten S. Vannice [a,1], Annelies Wilder-Smith [a,b,1], Alan D.T. Barrett [c,1], Kalinka Carrijo [d,1], Marco Cavaleri [e,1], Aravinda de Silva [f,1], Anna P. Durbin [g,1], Tim Endy [h,1], Eva Harris [i,1], Bruce L. Innis [j,1], Leah C. Katzelnick [i,1], Peter G. Smith [k,1], Wellington Sun [l,1], Stephen J. Thomas [h,1], Joachim Hombach [a,1,*]

[a] World Health Organization, Department of Immunizations, Vaccines and Biologicals, Geneva, Switzerland
[b] Lee Kong Chian School of Medicine, Singapore
[c] Sealy Center for Vaccine Development and World Health Organization Collaborating Center for Vaccine Research, Evaluation and Training for Emerging Infectious Diseases, University of Texas Medical Branch, Galveston, TX, USA
[d] Brazilian Health Regulatory Agency – Anvisa, Brasília, DF, Brazil
[e] European Medicines Agency, London, United Kingdom
[f] Department of Microbiology and Immunology, University of North Carolina School of Medicine, Chapel Hill, NC, USA
[g] Center for Immunization Research, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA
[h] State University of New York, Upstate Medical University, Syracuse, NY, USA
[i] Division of Infectious Diseases and Vaccinology, School of Public Health, University of California, Berkeley, Berkeley, CA, USA
[j] Respiratory Infections and Maternal Immunizations, PATH Center for Vaccine Innovation and Access, Washington, DC, USA
[k] Tropical Epidemiology Group, London School of Hygiene & Tropical Medicine, London, United Kingdom
[l] Food and Drug Administration, Silver Spring, MD, USA

ARTICLE INFO

Article history:
Received 16 November 2017
Received in revised form 5 February 2018
Accepted 15 February 2018
Available online 7 March 2018

Keywords:
Dengue
Dengue vaccine
Vaccine clinical trials
Vaccine regulation
Enhancement

ABSTRACT

Licensing and decisions on public health use of a vaccine rely on a robust clinical development program that permits a risk-benefit assessment of the product in the target population. Studies undertaken early in clinical development, as well as well-designed pivotal trials, allow for this robust characterization. In 2012, WHO published guidelines on the quality, safety and efficacy of live attenuated dengue tetravalent vaccines. Subsequently, efficacy and longer-term follow-up data have become available from two Phase 3 trials of a dengue vaccine, conducted in parallel, and the vaccine was licensed in December 2015. The findings and interpretation of the results from these trials released both before and after licensure have highlighted key complexities for tetravalent dengue vaccines, including concerns vaccination could increase the incidence of dengue disease in certain subpopulations. This report summarizes clinical and regulatory points for consideration that may guide vaccine developers on some aspects of trial design and facilitate regulatory review to enable broader public health recommendations for second-generation dengue vaccines.

1. Introduction

The first dengue vaccine (CYD-TDV or Dengvaxia®, by Sanofi Pasteur) was licensed in December 2015, after decades of research and clinical development. Despite a significant global demand, dengue vaccine development has been difficult for several reasons, including the need for a tetravalent vaccine with efficacy against each of the four dengue virus (DENV) serotypes, the lack of

* Corresponding author at: Department of Immunization, Vaccines and Biologicals, World Health Organization, CH-1211 Geneva 27, Switzerland.
E-mail address: hombachj@who.int (J. Hombach).
[1] All authors attest they meet the ICMJE criteria for authorship.

https://doi.org/10.1016/j.vaccine.2018.02.062
0264-410X/

representative animal models, and concerns about vaccine-induced immune enhancement as seen in natural infection [1,2]. While the successful registration of the first dengue vaccine represented a major milestone, there have also been setbacks. First, the results of the multi-center pivotal Phase 3 trials highlighted important limitations [3,4]. In these trials, in which three vaccine doses were given separated by six months, efficacy varied according to serotype, age and baseline dengue serostatus. Because a safety signal was observed in young children in one of the trials during longer-term follow-up, children below 9 years of age were subsequently excluded from the age-indication of this vaccine. In April 2016, the World Health Organization (WHO) recommended countries consider introducing the first licensed dengue vaccine only in settings with a high burden of dengue disease, for the age group of 9–45 years, with seroprevalence criteria in the target age group for vaccination of ideally >70% [5]. WHO issued this recommendation due to limited evidence supporting the efficacy, safety, and long-term performance of the vaccine in DENV-seronegative individuals age >9 years, concerns about an excess risk of hospitalized dengue in younger (2–5 years old) subpopulations, and lower efficacy in DENV-seronegative subpopulations included in the current license [6]. WHO and advisors called on the company to further interrogate the clinical trial data and conduct additional targeted studies to further analyze the issue of safety and risk for increased incidence of symptomatic infection among vaccinated seronegative persons, to be done as soon as possible [5–7]. A proposal for the necessary post-licensure studies to address the question of safety in seronegatives, including study designs, has been published [8].

On November 29, 2017, Sanofi Pasteur announced that it had used a new NS1 assay on sera taken after the 3rd dose and imputation methods in order to classify participants retrospectively into those likely to have been seronegative or seropositive at the time of the first vaccine dose. These results were used to estimate the long-term safety and efficacy of the vaccine by serostatus prior to vaccination [9]. The company found an increased risk of severe and hospitalized dengue associated with vaccination among seronegatives. The company has stated its intention to change the label so that individuals who have not been previously infected by dengue virus should not be vaccinated. The WHO Global Advisory Committee on Vaccine Safety and the WHO Secretariat published interim statements on December 7, 2017 [10], and December 22, 2017 [11], respectively. A full evidence review is now underway to revise the WHO position.

In 2012, WHO issued guidelines on the regulation of dengue vaccines, including their clinical development [12]. In light of the experience of clinical development and of trying to formulate evidence-based policy-making for the first licensed dengue vaccine, WHO convened a group of independent experts on March 21, 2017, to develop points for consideration for the clinical evaluation of second-generation dengue vaccines. Here we summarize the discussions and recommendations from this ad hoc consultation, which took place before the Sanofi Pasteur announcement, but the points for consideration are all the more relevant in light of the new information. These reflections, summarized in Box 1 may help vaccine developers, regulators and public health decision-makers in planning studies or evaluating data on dengue vaccines. It does not replace original WHO guidance [12], but provides additional perspectives.

Box 1 Points for consideration for the development of second-generation live attenuated dengue vaccines.

- Early clinical studies are valuable to evaluate the potential for interference between individual vaccine viruses and the impact on the development of type-specific versus heterotypic immunity.
- Measuring antibody neutralization activity remains the best method of defining dengue vaccine immunogenicity; however, current assays do not easily distinguish between type-specific antibodies, transient heterotypic antibody, and long-lasting heterotypic antibody. Given this uncertainty, the critical time point for assessment of immunogenicity as a correlate of durable protection should be more than 12 months after the last vaccine dose. Various research assays may be complementary.
- Controlled Human Infection Model (CHIM) trials can provide initial proof-of-concept that a vaccine may have potential for clinical benefit, but greater confidence is required in Dengue CHIM performance and challenge should be complete 12 months or more after the last vaccine dose.
- For licensure, in the absence of an accepted correlate of protection or risk, vaccine efficacy will need to be demonstrated based on clinical outcomes collected over a multi-year period (multiple dengue seasons) that support durable benefit.
- Pre-vaccination and post-vaccination blood samples should be collected and sera stored from all trial participants.
- Dengue serostatus at baseline is a critical variable, and safety and efficacy by serostatus should be presented in a stratified analysis.
- Active surveillance used to assess efficacy against all dengue disease and severe dengue disease should be in place preferably for at least 3–5 years after the last vaccine dose.
- Immunogenicity and efficacy results should be interpreted in the context of potential transient heterotypic immunity that could wane over time.

2. Findings from the trials of the first-generation dengue vaccine

The first licensed dengue vaccine, CYD-TDV or Dengvaxia®, is a recombinant live attenuated, tetravalent dengue vaccine based on the yellow fever 17D vaccine backbone. The structural genes (prM-E) of the YF17D virus vector are replaced by the structural genes of each the four DENV serotypes. The initial license was typically with an indication for individuals aged 9–45 years living in endemic areas. Licensure was based on two large multicenter Phase 3 trials conducted in Asia and Latin America with over 30,000 trial participants; serostatus at baseline was assessed in a subset of about 2000 subjects in each trial [3,4,13]. A post hoc analysis stratifying vaccine efficacy and safety by <9 and ≥9 years of age across all trials led to the age indication starting at 9 years of age even though two efficacy trials enrolled down to 2 or 4 years of age. CYD-TDV is now registered in 19 countries [14].