DENGUE VACCINE DEVELOPMENT AND VALIDATION TIMELINE

Last updated: June 2018

1993

Sanofi Pasteur begins pursuit of a dengue vaccine.

2002

WHO publishes guidelines for the clinical evaluation of dengue vaccines in endemic areas[1].

2004

Sanofi Pasteur begins clinical development of its current live attenuated vaccine.

2007

Positive and balanced immunogenicity results against the 4 DENV serotypes in phase II clinical studies confirm proof of concept for the dengue vaccine candidate.

2008

WHO updates its Guidelines for clinical evaluation of dengue vaccines in endemic areas. The Guidelines indicate that any dengue vaccine candidate should show efficacy against laboratory-confirmed dengue illness, resulting from at least one of the four serotypes[4]. The ultimate long-term objective for a tetravalent vaccine, and a major challenge, will be to demonstrate protective efficacy against each of the four dengue virus serotypes in the absence of any long-term safety concerns. This long-term safety evaluation is based on complexity of dengue infection given that the secondary infection with a dengue virus tends to be worse than the first infection.

2009

The Sanofi Pasteur dengue vaccine candidate enters a clinical efficacy study among 4,002 children aged 4 – 11 years old in Thailand (Phase IIb CYD23).

JUNE 2010

An Independent Data Monitoring Committee (IDMC) reviews clinical data on the vaccine coming from the ongoing Phase IIb trial and supports the decision to initiate Phase III studies with the vaccine.

JUNE 2011

The dengue vaccine candidate enters two phase III clinical studies in endemic countries where dengue is identified as a public health priority: 5 countries in Asia (CYD 14, including 10,275 people 2-14 years old in Thailand, the Philippines, Vietnam, Malaysia, Indonesia) and Latin America (CYD 15, including 20,869 people 6 – 19 years old in Puerto Rico, Honduras, Mexico, Colombia, Brazil).

Phase III trials consist of a first 25-month period over which investigators study efficacy and safety to reach primary study endpoints required for regulatory submission and a second, additional 4 year study period to follow up on the vaccine's long-term safety as recommended by the WHO guidelines.

Phase III studies begin prior to the close of the Phase IIb study in Thailand based on IDMC review, strong immunogenicity data on the vaccine, need for large-scale evaluation of clinical efficacy and safety for regulatory filing, and no indication of any safety concerns. US FDA oversaw study protocol and endpoints for efficacy and safety given that the study program includes the US territory of Puerto Rico as a trial site.

JULY 2012

Results from Sanofi Pasteur's phase IIb clinical trial in Thailand published in The Lancet demonstrated for the first time that a safe dengue vaccine is achievable[2].

AUGUST 2012

WHO publishes its Global Strategy for Dengue Prevention and Control and solicits input from its Technical Advisory Group (TAG) on dengue vaccines in late stage development which begins providing ongoing advice to WHO on key topics to evaluate in dengue vaccine development[3].

JULY 2014

CYD14, Phase III 25-month safety and efficacy study in Asia demonstrated vaccine efficacy against dengue disease, including hospitalization and severe disease. No safety signal observed in this 25-month period. Results published online in *The Lancet*[5].

NOV. 2014

CYD15, Phase III 25-month safety and efficacy study in Latin America demonstrated protection against all of the four dengue serotypes and all severities of dengue. No safety signal observed in the 25-month period. Results published online in the *New England Journal of Medicine*[6].

APRIL 2015

The WHO's TAG transitions its oversight to the Strategic Advisory Group of Experts on Immunization (SAGE) which picks up review of the data available at that time, including all Sanofi Pasteur data (Phase IIb and the two Phase III efficacy and safety studies)[7].

The SAGE exchanges with 4+ external advisory committees. Among these are the Global Advisory Committee on Vaccine Safety (GACVS), the Immunization and Vaccines related Implementation Research Advisory Committee (IVIR-AC), the Immunization Practices Advisory Committee (IPAC), and the Comparative Modelling of Dengue Vaccine Public Health Impact (CMDVI). An independent group of experts develop 8 models to assess the impact of introducing the vaccine in public vaccination programs in order to inform the WHO vaccine review process. All 8 modelled outcome studies, which account for the possibility that the vaccine could act as a silent infection due to the complexity of dengue, show an overall positive public health benefit of introducing the vaccine in public programs targeting high prevalence populations (NOTE: These results serve as basis for the WHO 2016 position on the vaccine recommending its use be targeted to populations with 70% or higher dengue seroprevalence)[8,9].

JULY 2015

The Dengue Vaccine Initiative (DVI) and WHO convene a meeting with seven dengue-endemic country National Regulatory Authorities and the US Federal Drug Administration and the European Medicines Agency for joint technical consultations of the regulatory file for the vaccine including all Phase IIb and Phase III pooled efficacy and 3-year safety data. The meeting seeks to clarify any questions on the available data on the vaccine and support a novel strategy to seek first approval and access to the vaccine in countries where dengue represents a major public health priority[10].

The New England Journal of Medicine publishes online the Pooled Phase III efficacy and safety results showing that Sanofi Pasteur's vaccine candidate safely protects study participants 9-16 years old over a 25 month period, with extrapolation to adult ages based on other study data including populations up to 60 years of age, against all dengue serotypes and severities[11]. The publication also reports integrated safety results from the ongoing Phase IIb and Phase III study programs that show a safety signal in the 2 – 5 year old age group during the 3-year follow up of CYD 14 Phase III Asian study only.

No safety signal is observed in any of the other age groups in the CYD14 study or in any of the other studies. Baseline serostatus was documented for 10 - 20% of the CYD14 and CYD15 studies populations allowing for assessment of vaccine efficacy in this subgroup which was reported to be 52.3% for people without prior dengue infection (seronegatives) and 80% for people with a prior dengue infection (seropositives). Blood samples were not taken on all study participants as this was considered unethical given that there was no scientific basis for this established at the time. The clinical results reported in this publication serve as the basis for the recommended indication of 9 years old and older for registration of the dengue vaccine.

DEC. 2015

Sanofi Pasteur's Bruno Guy and Nick Jackson publish a study in Nature Reviews Microbiology that provides several hypotheses to understand CYD-TDV mode of action. The authors acknowledge the unknowns around the vaccine's impact in seronegative individuals. The authors propose a theory about the impact of age and immune status on vaccine's performance profile[12].

The vaccine received its first 3 license registrations in Mexico, the Philippines and Brazil.

APRIL 2016

Following a process of national expert consultations and recommendation-making, the Philippines begins the first public vaccination program targeting 3 regions with dengue seroprevalence estimated to be 85% or higher; i.e. where more than 8 out of every 10 person has had a prior dengue infection[13].

SAGE issues recommendation to the WHO that vaccination be considered as part of integrated disease control and prevention programs in highly endemic settings of 70% or higher.

JULY 2016

WHO issues its position paper on the vaccine following the recommendation of the April SAGE that countries consider vaccination in areas with high dengue transmission. WHO also requests that Sanofi Pasteur further evaluate the vaccine's long-term safety in individuals without a prior dengue infection (aka seronegatives). Sanofi Pasteur immediately begins investigating how to retrospectively evaluate the Phase III clinical data to take a closer look at the potential impact of prior dengue infection on vaccine performance.

2016 2017

Sanofi Pasteur continues conducting and publishing long-term follow-up results from Phase IIb and Phase III trials with close oversight by the IDMC. Documentation shows a persistent reduction in risk of hospitalization due to dengue in study participants 9 years of age and older for up to 6 years post dose 1[14,15,16,17,18].

Sanofi Pasteur leverages an existing collaboration with the University of Pittsburg in the US in order to accelerate development of a new assay test that will allow the company to conduct a supplementary analysis to assess the potential impact of prior dengue infection on vaccine performance using the clinical data that has been collected on Phase IIb and Phase III study participants for up to 5 years post initial dose.

NOV. 2017

Sanofi Pasteur shares results of the supplementary analysis with National Regulatory Agencies of the countries where the vaccine is approved for use, recommending an update to the prescribing information for the vaccine. Sanofi also communicates the topline results publically in a global company statement.

The proposed label update from the company recommends that healthcare professionals assess the likelihood of prior dengue infection in an individual before vaccinating: The vaccine provides long-term protective benefit against dengue fever in those who had prior dengue infection. For individuals who have not been previously infected by dengue virus, vaccination should not be recommended. Vaccination should only be recommended when the potential benefits outweigh the potential risks (in countries with high burden of dengue disease). All regulatory authorities where the vaccine is approved or under regulatory consideration begin assessment of new data and proposed label update[19, 20].

DEC. 2017

The Philippines halts its public vaccination program citing the need to further review the new data on the vaccine with external experts, including the WHO.

In Brazil, Parana State health authorities indicate intention to move forward with a fourth wave of public vaccination program to ensure coverage with all 3 doses of the vaccine in target population living in 30 municipalities where dengue burden is high (no first vaccinations to be offered); Brazil regulatory authority (ANVISA) posts a Q&A on the new data on the dengue vaccine and acknowledges the public health value of continuing the Parana State public program.

The WHO issues an updated Q&A on the vaccine[21] and kicks off a new cycle of review for the vaccine; updated SAGE recommendation expected 18th April, followed by new WHO position paper by June/July, 2018.

MARCH 2018

Journal *Vaccine* publishes WHO-authored paper on new considerations for next generation dengue vaccines based on important long-term clinical documentation on the Sanofi Pasteur dengue vaccine[22].

4th wave of Parana State dengue vaccination program in Brazil implemented to increase coverage rates for 3-dose regimen; no new vaccinations are offered.

APRIL 2018

The Strategic Advisory Group of Experts (SAGE) on Immunization communicated an updated recommendation to the WHO which confirms the public health value of the dengue vaccine in high endemic populations. The SAGE recommended two options. The preferred is a 'prescreen & vaccinate' option which would use currently-available serotests, despite limitations. The SAGE also recommends another option of vaccinating without individual prescreening in very high endemic settings (80% seroprevalence at 9 years of age).[23]

JUNE 2018

The New England Journal of Medicine publishes Impact of Dengue Serostatus on Dengue Vaccine Safety and Efficacy with full analysis of supplementary data which formed the basis of Sanofi Pasteur's label update request to National Regulatory Authorities in November 2017. Publication documents that the vaccine prevents 76% of all dengue infections and reduces severe dengue incidence by 84% and hospitalizations due to dengue by 80% in individuals with prior dengue infection before vaccination. Vaccination is not recommended in individuals without prior infection as it can lead to an increased risk of severe dengue if a person is infected post-vaccination. The level of risk in these vaccinated people without a prior infection is no greater than that for unvaccinated people who get a secondary infection. All vaccinated individuals who got severe dengue recovered fully following symptomatic medical care.»

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