



**Department of Health and Human Services  
Food and Drug Administration  
Center for Biologics Evaluation and Research**

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**MEMORANDUM**

**Date:** 17 September 2018

**To:** 125682/0

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**Through:** Adamma Mba-Jonas, MD  
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**Re:** Pharmacovigilance Plan assessment for Dengvaxia (tetravalent, live attenuated dengue vaccine)

## 1. OBJECTIVE

To evaluate the adequacy of the Pharmacovigilance Plan (PVP) proposed by the sponsor for the postmarketing safety surveillance of Dengvaxia.

## 2. INTRODUCTION

### 2.1 Background

Dengue is a mosquito-borne viral illness endemic to tropical and subtropical parts of the world including countries in Africa, the Caribbean, Asia and Latin America. Nearly all dengue cases reported in the 48 continental states are acquired elsewhere by travelers or immigrants – most dengue cases in U.S. citizens occur in Puerto Rico, the U.S. Virgin Islands, Samoa and Guam, where the virus is endemic.<sup>1</sup> Of the 4 U.S. regions where dengue is endemic, Puerto Rico has by far the largest population at about 3.3 million people.<sup>2</sup>

Dengue virus is a ribonucleic acid (RNA) flavivirus with four antigenically distinct serotypes. Infection with one dengue serotype is generally believed to confer life-long immunity to that serotype (homotypic protection) while cross-immunity to other serotypes (heterotypic protection) persists for one or two years.<sup>3</sup> Most dengue virus infections are asymptomatic or cause a mild illness, but a small proportion of cases develop severe disease manifested as plasma leakage, bleeding or severe organ involvement. Multiple epidemiological studies have shown that the risk of developing severe disease is higher after a heterotypic second dengue virus infection as compared to the risk following primary infection, – although the risk of severe dengue after secondary infection still remains relatively small (estimated 0.5%-2%).<sup>3</sup> Antibody-dependent enhancement of infection has been proposed as a possible underlying mechanism, although both viral and human host factors, such as age and ethnicity may play a role.<sup>3</sup>

Dengue disease epidemiology is complex due to several factors including geographic variations in population seroprevalence, the dominant circulating dengue serotype and the possible presence of other circulating flaviviruses. Other members of the flaviviridae include Zika, West Nile, Japanese encephalitis (JE) and yellow fever (YF) viruses. In addition, seroprevalence can vary by age group and the dominant circulating dengue serotype can vary with time. Furthermore, the clinical diagnosis of primary dengue can be difficult due to a mild or asymptomatic presentation without pathognomonic findings. Laboratory confirmation of dengue infection can be challenging particularly in geographic areas where more than one flavivirus is circulating, because of shared cross-reactivity. Antibodies directed against non-dengue flaviviruses can cross-react in dengue IgM or IgG serology assays, leading to false-positive results.<sup>4</sup> Alternative diagnostic laboratory tests include reverse transcriptase polymerase chain reaction (RT-PCR) tests for dengue viral RNA or tests to detect the dengue specific non-structural protein 1 antigen (NS1). While RT-PCR for viral RNA is sensitive, specific and fast, it

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<sup>1</sup> Centers for Disease Control and Prevention. Dengue epidemiology.

<https://www.cdc.gov/dengue/epidemiology/index.html> Accessed 17Sep2018

<sup>2</sup> United States Census Bureau. Quick Facts- Puerto Rico. Population estimates, July 1, 2017, (V2017).

<https://www.census.gov/quickfacts/geo/chart/pr/PST045217> Accessed 16Apr2019

<sup>3</sup> Wichmann O, Vannice K, Asturia EJ *et al* Live-attenuated tetravalent dengue vaccines: The needs and challenges of post-licensure evaluation of vaccine safety and effectiveness. *Vaccine* 35 (2017) 5535–5542

<sup>4</sup> Muller DA, Depelsenaire ACI and Young PR. Clinical and Laboratory Diagnosis of Dengue Virus Infection, *J Inf Dis* Volume 215, Issue suppl\_2, 1 March 2017, Pages S89–S95

requires specialized equipment and trained staff – as a result RT-PCR may not be widely or immediately available. Highly specific dengue NS1 antigen-capture enzyme-linked immunosorbent assays (ELISAs) and immunochromatographic rapid strip tests have been designed with no demonstrable cross-reactivity with other flavivirus NS1 species, although possible cross-reactivity with Zika has yet to be fully evaluated.<sup>4</sup> Of note, while a highly specific point-of-care rapid diagnostic test (RDT), would facilitate the implementation of a pre-vaccination screening strategy, to date none have been validated or licensed specifically for the detection of past dengue infection.<sup>5</sup>

## **2.2 Product Information**

Dengvaxia is a prophylactic, tetravalent, live attenuated viral vaccine containing each of the four dengue serotypes. Each of the four viruses is obtained separately using recombinant DNA technology to replace the sequences encoding the premembrane (prM) and envelope (E) proteins in the yellow fever YF17D204 virus genome with those encoding the homologous dengue sequences.<sup>6</sup>

The proposed indication states that the product should be used in individuals 9 through 16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas. Previous dengue infection can be assessed through a medical record of a previous laboratory confirmed dengue infection or through serological testing prior to vaccination. In addition, Dengvaxia is not recommended in persons who have not been previously infected by any dengue virus or for whom this information is not known. The vaccine is supplied as a lyophilized powder to be reconstituted with the supplied diluent for a 3-dose immunization series consisting of a 0.5 mL subcutaneous injection administered at 6-month intervals (month 0, 6, and 12).<sup>6</sup>

## **2.3 Regulatory History**

### **2.3.1 U.S. Regulatory History**

On 21Dec2016 Sanofi Pasteur submitted the original BLA for Dengvaxia to FDA (125645/0). At that time the proposed indication was the prevention of dengue disease caused by all four dengue virus serotypes in individuals 9 through 45 years of age living in endemic areas, with no proposed limitation of use to individuals who are seropositive for dengue from prior infection. The BLA was voluntarily withdrawn by the sponsor on 01Feb2017 for dataset formatting and compilation (125645/0.2).

On 31Aug2018 the BLA was resubmitted to FDA (125682/0). The new proposed indication includes a statement for use only in laboratory-confirmed seropositive individuals. Initially, the proposed age indication in the resubmitted BLA remained the same as prior – individuals aged 9 through 45. However, on 7Mar2019, at the Vaccines and Related Biological Products Advisory Committee (VRBPAC) Meeting on Dengvaxia, the committee voted more favorably on the safety and effectiveness of the data for individuals aged 9 to <17 compared to 9 through 45.<sup>7</sup> On

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<sup>5</sup> World Health Organization. Dengue vaccine: WHO position paper, September 2018 – Recommendations. *Vaccine* 2018 Nov 10. pii: S0264-410X(18)31339-2. doi: 10.1016/j.vaccine.2018.09.063. [Epub ahead of print]

<sup>6</sup> Sanofi. Dengvaxia. Draft labeling text. 8Apr2018 125682/0.42

<sup>7</sup> FDA. Vaccines and Related Biological Products Advisory Committee 03.06.19-.03.07.19-Meeting-Summary-Minutes.pdf Available at

1Apr2019, Sanofi decided to seek licensure only in individuals aged 9 through 16. The PVP of the resubmitted BLA is the subject of this review.

### 2.3.2 International Regulatory History

The sponsor reports that the first marketing authorization for Dengvaxia was obtained in Mexico on 8Dec2015.<sup>8</sup> Since then, the product has been approved in 21 countries including Australia on 20Jul2017 and most recently, on 19Oct2018, marketing authorization for Dengvaxia was granted by the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP).<sup>9</sup> The Philippines suspended Dengvaxia for one year effective 03Jan2018.<sup>8</sup> The sponsor reports that the Philippines suspension of Dengvaxia “is linked to an alleged failure to comply with post-marketing requirements and is not linked to the product profile.”<sup>8</sup> International postmarketing data submitted by the sponsor is reviewed in section 2.4.1 below.

### 2.4 International Postmarketing Data

International postmarketing data has been submitted by the sponsor and is reviewed in section 2.4.1 below. Additional international postmarketing data has been obtained from the European Medicine’s Agency (EMA) and Australia’s Therapeutic Goods Association (TGA) and is reviewed in section 2.4.2.

#### 2.4.1 International Postmarketing Data - Sanofi

The sponsor reports that cumulatively, from initial marketing authorization to 31Aug2018, a total of (b) (4) doses have been distributed worldwide with the majority of doses distributed through public programs in the Philippines and Brazil. A total of 2770 (487 serious and 2283 non-serious) adverse events have been reported to Sanofi Pasteur in the post-marketing setting as of 14Sep2018. The sponsor has provided a breakdown of all post-marketing AEs reported to Sanofi by country and age in Tables 1 and 2 below.

Table 1. Dengvaxia Adverse Event Reports received by Sanofi by Country as of 14Sep2018

Country of Reporter	Death (n)	Non-fatal Serious (n)	Non-serious (n)	Total (n)
BRAZIL	5	135	951	1091
COSTA RICA	0	0	13	13
EL SALVADOR	0	0	1	1
GUATEMALA	0	0	1	1
INDONESIA	0	1	12	13
MALAYSIA	0	0	1	1
MEXICO	0	1	14	15
PARAGUAY	0	0	2	2

<https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/ucm630701.htm>

<sup>8</sup> Sanofi Pasteur. Safety Information Amendment, 19Oct2018. 125682/0.8

<sup>9</sup> European Medicines Agency, 19Oct2018 Press Release: First Vaccine for Prevention of Dengue.

<https://www.ema.europa.eu/en/news/first-vaccine-prevention-dengue>

PERU	0	7	33	<b>40</b>
PHILIPPINES	46	281	1221	<b>1548</b>
SINGAPORE	0	0	3	<b>3</b>
THAILAND	0	10	31	<b>41</b>
UNITEDSTATES <sup>†</sup>	0	1	0	<b>1</b>
<b>TOTAL</b>	<b>51</b>	<b>436</b>	<b>2283</b>	<b>2770</b>

<sup>†</sup>Represents a social media report in the U.S. regarding an event in an unknown country

**Table 2. Adverse Event Reports received by Sanofi Pasteur for Dengvaxia by Age Group as of 14Sep2018**

Age of vaccinee (yr)	Death (n)	Non-fatal Serious (n)	Non-serious (n)	Total (n)
<9 <sup>†</sup>	1	3	55	59
≥9 to <18	28	281	1283	1592
≥18 to ≤45	5	89	533	627
>45	0	4	107	111
Age unreported	17	59	305	381
All ages	51	436	2283	2770

<sup>†</sup>Cases of exposure in utero or during breastfeeding are included. If age is unknown it is listed as unspecified.

Sanofi Pasteur reports that in November 2017, the number of reported deaths increased after public communication about the increased risk of severe and/or hospitalized dengue following vaccination in individuals not previously infected by dengue virus. The sponsor specifically notes that in the Philippines, the number of reported cases of dengue with fatal outcomes also increased following multiple media reports and press releases. However, there was no information on serostatus prior to vaccination available for those cases.<sup>8</sup>

Individual Case Safety Reports (ICSR) for all 51 deaths have been submitted by Sanofi.<sup>10</sup> Of the 51 fatal reports, 33 deaths occurred in individuals aged 9 to 45 years of age. All 33 reports were individually reviewed and the Centers for Disease Control and Prevention (CDC) 2015 case definition for dengue virus infections<sup>11</sup> was applied. Eleven of 33 death reports met the case definition of Severe Dengue, 1 in Brazil and 10 in the Philippines. The 10 reports from the Philippines list individuals aged 10-13 and the single report from Brazil is of a 27 year old woman. Of the 11 reports of Severe Dengue - 2 met the CDC case definition of *confirmed* Severe Dengue (both in the Philippines) and 9 met the case definition for *suspected* Severe Dengue.

<sup>10</sup> Sanofi. Suspect Adverse Reaction Reports - Batch of 51 Fatal Dengvaxia Cases - CIOMS Reports 19Oct2018 125682/0.8

<sup>11</sup> Centers for Disease Control and Prevention Dengue Virus Infections 2015 Case Definition. Available at <https://wwwn.cdc.gov/nndss/conditions/dengue-virus-infections/case-definition/2015/>

#### 2.4.1.1 Postmarketing Experience – Philippines.

The sponsor reports that overall, approximately 835,000 individuals have received at least one dose of Dengvaxia during public immunization programs in the Philippines. The sponsor describes 4 school or community-based programs in which all vaccinees were aged 9 years and above. In addition, Sanofi reports that a robust surveillance system was put in place by the Philippine Department of Health (DH) at the start of the campaign in March 2016, with the collection of all adverse events following immunization (AEFI) including causality assessment following review by an AEFI committee.<sup>8</sup>

In November 2017, after the update on the results of the supplemental analysis from Sanofi Pasteur to the Philippines FDA on the increased risk of hospitalized and/or severe dengue in individuals not previously infected by dengue, the Philippines DH established an increased surveillance of adverse events among Dengvaxia vaccinees and issued an interim guideline on 09Feb2018 with the following objectives:

- (1) identifying and immediately reporting vaccinated individuals who have died or were ill and admitted to health facilities
- (2) determining the post-vaccination adverse events and diseases among Dengvaxia vaccinees
- (3) providing strategic information to help improve the efficiency of referral systems and to enhance the clinical management of Dengvaxia vaccinees who become ill.

The DH plans surveillance of adverse events among Dengvaxia vaccinees for a minimum of 5 years from the date of first vaccination, with reporting by health professionals, facilities and vaccinees or guardians of vaccinees.<sup>12</sup>

#### 2.4.1.2 Postmarketing Experience – Brazil

In Brazil, the sponsor describes public vaccination programs where all vaccinees were between 9–44 years of age. It is estimated that around 300,000 individuals aged between 15–27 years of age received at least 1 dose of Dengvaxia during the Parana State public vaccination program where the surveillance system was enhanced in preparation for the campaign. A guideline was developed, and training performed by the local authorities, online real-time report was instituted and mandatory reporting for all AEFI were requested. Laboratory confirmation of suspected dengue cases became mandatory and laboratory capacity was improved with the use of PCR and NS1 Ag testing for case confirmation in those vaccinated. An active surveillance system to monitor dengue cases among vaccinees was also implemented using linkages between immunization records database and Brazil's Information System for Notifiable Diseases, also known as SINAN (Sistema de Informação de Agravos de Notificação). Weekly data exchanges about AEFI are ongoing between the Parana DH and Sanofi Pasteur as per mutual agreement.<sup>8</sup>

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<sup>12</sup> Sanofi. Republic of the Philippines, Department of Health. OFFICE OF THE SECRETARY. FEB 09 2018 ADMINISTRATIVE ORDER. No. 2018-0004. SUBJECT: Interim Guidelines on the Surveillance of Adverse Events among Dengvaxia Vaccinees (AEDV Surveillance). 125682/0.14

## **2.4.2 International Postmarketing Data – Regulatory Agencies**

### **2.4.2.1 Postmarketing Experience – European Medicines Agency**

On 19Oct2018, initial marketing authorization for Dengvaxia was granted by the European Medicines Agency (EMA), with marketing authorization later made valid throughout the European Union on 12Dec2018.<sup>13</sup> The therapeutic indication authorized by the EMA for Dengvaxia is “for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in individuals 9 to 45 years of age with prior dengue virus infection and living in endemic areas.”<sup>7</sup> Given the recent approval, the current postmarketing experience in the EU is limited.

### **2.4.2.2 Postmarketing Experience – Australia’s Therapeutic Goods Association**

Information regarding Australia’s postmarketing experience with Dengvaxia was obtained from the Therapeutic Goods Association (TGA) under the terms of a confidentiality arrangement. The TGA reports that in Australia, (b) (3)

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## **3 CLINICAL SAFETY DATABASE**

The sponsor has submitted two Phase III randomized controlled efficacy trials in support of the BLA – CYD14 and CYD15 (section 3.1.1). Sanofi has also submitted data from CYD23, a Phase IIb efficacy proof-of-concept study (and the follow-up study CYD57) in support of the BLA (section 3.1.2). Of note, pre-vaccination serostatus assessment were not required for all study subjects. In the three studies CYD 14, CYD 15 and CYD23/57, blood samples were collected prior to vaccination for only a subset of subjects, designated as the “immunogenicity subset.” Also of note, study subjects in CYD14, CYD15 and CYD23/57 were all children and/or adolescents. For this reason, additional data from 3 additional trials conducted in adults (CYD22, CYD28, and CYD47) were submitted by Sanofi to support the originally requested age indication of 9 to 45 years of age (section 3.2).

### **3.1 Safety Data in Children and Adolescents**

#### **3.1.1 CYD14 and CYD15**

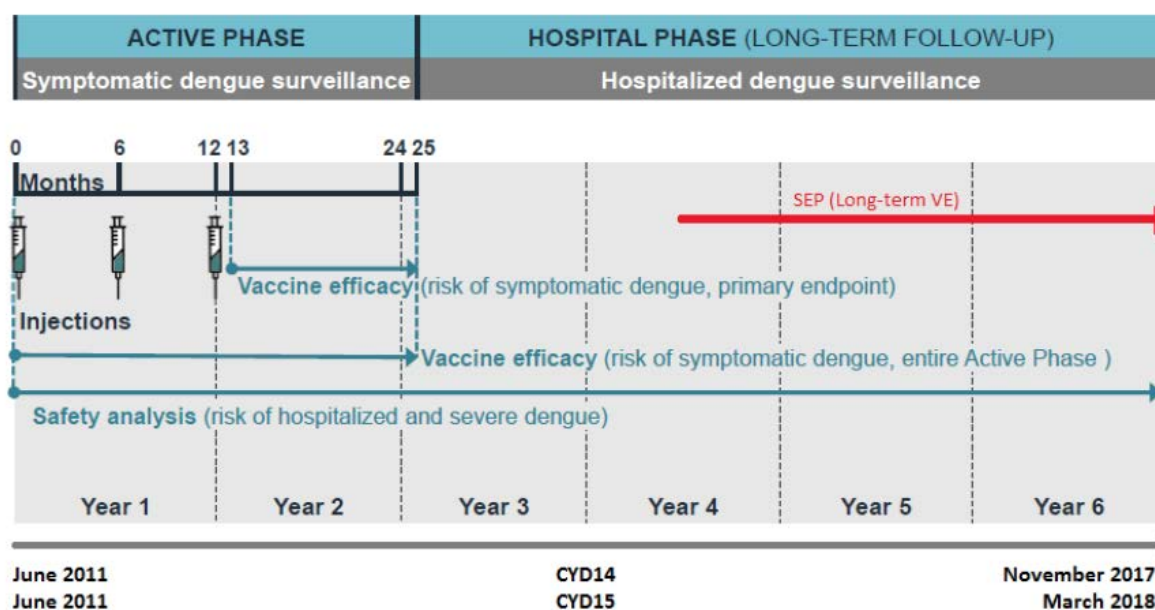
CYD14 and CYD15 are Phase III randomized controlled trials. CYD14 was conducted in the Asia-Pacific region in 2 to 14 year olds, and CYD15 was conducted in 5 countries in Latin America in 9 to 16 year olds. Of the two studies, only CYD15 included study subjects in an endemic area of the U.S. – Puerto Rico. For both studies, the objectives were to assess vaccine efficacy, safety and immunogenicity. CYD14 and CYD15 have the same study design, summarized in Figure 1 below. The study design includes 3 time periods:

<sup>13</sup> European Medicines Agency. Dengvaxia. Available at <https://www.ema.europa.eu/en/medicines/human/EPAR/dengvaxia#authorisation-details-section>

<sup>14</sup> Therapeutic Goods Association, Australia. Private Communication. December 12, 2018

- The Active Phase (M0-M25), in which surveillance was designed to maximize the detection of all symptomatic virologically confirmed dengue (VCD) by contacting parents or guardians of study subjects at least once a week.
- The Hospital Phase (M25 to the end of the trial), in which dengue screening occurred in febrile individuals who required hospitalization. Both hospitalized VCD and severe hospitalized VCD cases were to be collected up to 5 years after the third injection. Parents or guardians of study subjects were contacted at least once every 3 months. A safety signal was detected during Year 3 of the study when analyses by age group in CYD14 showed an imbalance of hospitalized VCD cases in individuals aged 2 to 5 years old between the Dengvaxia (n=15) and Control (n=1) groups. A similar imbalance was also observed in Year 3 in the same age group for hospitalized severe VCD with 6 cases observed in the Dengvaxia group and none in the Control group. These imbalances persisted during both Year 4 and 5. Over the 3-year period, the relative risk (RR) against hospitalized VCD was 2.108 (95% CI: 1.14; 4.21), and the RR against hospitalized severe VCD cases during the same period was 4.234 (95% CI: 1.01; 37.79).
- The Surveillance Expansion Phase (SEP) was implemented after the safety signal was detected and involved a return to the active surveillance system that had been in place during the Active Phase. The SEP occurred for approximately the last 2 years of the CYD14 and CYD15 studies, Years 5 and 6 of the studies. Analyses performed by the sponsor to evaluate the safety signal are described in section 3.1.3 below.

Figure 1. Outline of CYD14 and CYD15 trial design and important timelines<sup>15</sup>



SEP=Surveillance Expansion Phase, VE=Vaccine Efficacy

<sup>15</sup> Sanofi. Dengvaxia - Tetravalent, Live-Attenuated Viral Vaccine against Dengue Serotypes 1, 2, 3 and 4 Briefing Document for the Vaccines and Related Biological Products Advisory Committee. Final Version 1.0 dated 04 February 2019. Available at <https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/BloodVaccinesandOtherBiologics/VaccinesandRelatedBiologicalProductsAdvisoryCommittee/ucm630701.htm>

Table 3. Summary of Study Design and Safety Related Results of CYD14 and CYD15.

Study Number:	CYD14	CYD15
Study Design:	Phase III randomized controlled trial	Phase III randomized controlled trial
Study Objectives:	Vaccine efficacy, Safety and Immunogenicity	Vaccine efficacy, Safety and Immunogenicity
Study Subjects [SafAS] (n)*:		
Total	10,272	20,854
Randomized 2:1      Dengvaxia	6848	13,915 (n=875 in PR <sup>^</sup> )
Placebo <sup>#</sup>	3424	6939 (n=440 in PR <sup>^</sup> )
Study Subjects Aged (y):	2 through 14	9 through 16
Study Location	Indonesia, Malaysia, Thailand, Philippines, Vietnam	Brazil, Colombia, Honduras, Mexico, Puerto Rico
Safety Results:	<u>Deaths</u> : 7 (0.1%) in Dengvaxia group vs 4 (0.1%) in Placebo group. <u>SAE</u> : 804 (11.7%) in Dengvaxia group vs 479 (14.0%) in Placebo group.	<u>Deaths</u> : 33 (0.2%) in Dengvaxia group vs 23 (0.3%) in Placebo group. <u>SAE</u> : 1494 (10.7%) in Dengvaxia group vs 790 (11.4%) in Placebo group

\*SafAS=Safety Analysis Subset, <sup>#</sup>Placebo=NaCl 0.9%, <sup>^</sup>PR=overall study population in Puerto Rico, SAE=Serious Adverse Event

There was no imbalance in deaths or serious adverse events (SAE) between the Dengvaxia and placebo groups in either CYD14 or CYD15. Of the 7 deaths in CYD14, 5 were due to motorcycle or vehicular accidents, 1 was due to assault and 1 due to cardiogenic shock following myocarditis. In CYD14, the most common SAEs reported within 28 days after any injections, were from the SOCs “Infections and infestations” (0.4% in the Dengvaxia Group and 0.5% in the Control Group) and include reports of Dengue Fever – 5 in the Dengvaxia group and 6 in the placebo group representing <0.1% and 0.2% of all SAEs respectively. Other commonly reported SAEs in CYD14 were from the SOCs “Injury, poisoning and procedural complications” (0.2% in each group), and “Nervous system disorders” (< 0.1% in the CYD Dengue Vaccine Group and 0.1% in the Control Group).

Of the 33 deaths in the Dengvaxia group in CYD15, 11 deaths were firearm or gunshot related, 5 were due to road traffic or vehicular accidents, 5 were due to assault or homicide, 4 due to acute respiratory disease or failure, 3 were due to poisoning or intoxication, and 1 each due to fall, renal failure, suicide, encephalitis and sudden death. In CYD15, the most common SAEs reported in the both the Active and the Hospital Phase were from the SOCs: “Infections and Infestations,” including 2.1% in the Dengvaxia Group and 2.7% in the Placebo Group in the Active Phase, and in the Hospital Phase 1.0% of the Dengvaxia group and 1.2% of the Placebo Group. Of the SAEs in this SOC, serious dengue disease was reported by 0.3% in the Dengvaxia Group and 0.7% in the Placebo Group during the Active Phase, and in the Hospital Phase 0.4% in the Dengvaxia group and 0.7% in the Placebo group.

### 3.1.2 CYD23/57

CYD23 was a Phase IIb efficacy proof-of-concept study conducted in Thailand. The study was initially planned to include an Active Phase (from the start of the trial to 13 months after the third injection) followed by a Passive Phase (from 13 months after the third injection to 3 years after

the third injection). However, Sanofi reports that following a request from Thailand's Ministry of Public Health Ethical Review Committee for Research in Human Subjects, CYD23 was stopped at the beginning of the Passive Phase and the 3-year immunogenicity and safety follow up were not done as initially planned in the CYD23 approved protocol. However, all CYD23 subjects were asked to enroll in CYD57, a long-term follow-up of hospitalized dengue and safety of CYD23 subjects up to 4 years after the end of the Active Phase.

In CYD23, each study arm consisted of two cohorts. In the Dengvaxia group, the first 100 subjects constituted cohort 1 while the remainder subjects entered cohort 2 and subjects in both cohorts received Dengvaxia. In the control arm the 50 subjects in cohort 1 received 1 injection of rabies vaccine and 2 injections of placebo and the remaining subjects in cohort 2 received 3 injections of placebo.

CYD57 involved passive surveillance of hospitalized dengue cases in CYD23 study subjects during a 4-year follow-up period. Any SAE related to a study procedure or related to a previous injection from CYD23, or any fatal SAE (even if unrelated) was reported to the sponsor. Safety related results for CYD23 and 57 are summarized in Table 4 below.

**Table 4. Summary of Safety Related Results of CYD23/57.**

<b>Study Number:</b>	<b>CYD23</b>	<b>CYD57</b>
Study Design:	Phase IIb Randomized controlled, single-center, observer blind	Single-center, 4-year safety follow-up of up CYD23 study subjects
Study Objectives:	Vaccine Efficacy, Immunogenicity, Safety	Describe the incidence of hospitalized VCD, SAE monitoring
Study Subjects (n):		
Total	3997 <sup>^</sup>	3203*
Randomized 2:1		
Dengvaxia	2666	2131
Control	1331	1072
Study Subjects Aged (y):	4 to 11	4 to 11
Study Location:	Thailand	Thailand
Safety Results:	<u>Deaths</u> : 1 (0.04%) in the Dengvaxia group and 4 (0.30%) in the control group <u>SAEs</u> : 366 (11.8%) of subjects in the Dengvaxia group vs 218 (13.2%) in the control group	<u>Deaths</u> : 3 (0.12%) in the Dengvaxia group and 2 (0.15%) in the control group <u>SAEs</u> : No related SAEs were reported

\*FupAS=Follow up analysis set, <sup>^</sup>SafAS=Safety analysis set

In CYD 23, the single death in the Dengvaxia group was due to a vehicular accident, whereas the 4 deaths in the control group were due to drowning, lymphoma and 2 events of severe head injury. Most SAEs reported in CYD23 were in the SOC Infections and infestations (7.5% in the Dengvaxia group and 8.7% in the control group), with the highest reported infections being gastroenteritis, pharyngitis and bronchitis.

Of the 5 deaths that occurred in CYD57, 3 deaths occurred in the Dengvaxia group (2 due to gunshot wounds and one due to a road traffic accident) and 2 occurred in the control group due to drowning and a road traffic accident.

### 3.1.3 NS1 Supplemental Study and Extension

To evaluate the safety signal of severe/hospitalized VCD that was detected in CYD14, the sponsor conducted the NS1 supplemental study. Because baseline prevaccination blood samples were not obtained for all subjects in CYD14, CYD15 and CYD23/57, the NS1 supplemental study used Month 13 (M13) samples as a surrogate of baseline dengue serostatus. A subset of M13 samples from subjects in CYD14, CYD15 and CYD23/57 were tested using an ELISA that measures total IgG antibodies against the dengue NS1 protein. According to the sponsor, this assay was chosen as it can differentiate immune responses resulting from Dengvaxia vaccination from those resulting from natural dengue infection because the vaccine construct utilizes a YF backbone containing the YF NS1 gene, not the dengue NS1 gene. An extension of the study was completed by Sanofi to address limitations of the original study identified by the sponsor including misclassification of baseline serostatus, potential problems with randomization and the possible introduction of bias by excluding data from M0-M13. Ultimately, Sanofi concluded from the study that in seropositives, there is a statistically significant decreased risk of hospitalized and severe dengue over the period of long-term follow-up (cumulative to M60 - M72). The sponsor additionally concluded that in seronegatives, there is a statistically significant increased risk of hospitalized and severe dengue over the same long-term follow-up period in the overall trial population. However, this increased risk was not statistically significant in subjects  $\geq 9$  years of age.<sup>16,17</sup>

### 3.2 Safety data in adults

Three studies conducted in dengue-endemic regions – CYD22 (Vietnam); CYD28 (Singapore), and CYD47 (India) – have been submitted by the sponsor to contribute immunogenicity data in support of the use of Dengvaxia in adults aged 18-45 years. CYD22 and CYD47 were randomized 2:1 Dengvaxia to control group, and CYD28 was randomized 3:1.

Table 5. Summary of Safety-related Results in CYD22, CYD28 and CYD47.

Study Number:	CYD22	CYD28	CYD47
Study Design:	Phase 2 randomized placebo controlled observer blind	Phase 2 randomized placebo controlled observer blind	Phase 2 randomized placebo controlled observer blind
Study Objectives:	Immunogenicity Safety	Immunogenicity Safety	Immunogenicity Safety
Study Subjects age:	2 through 45y	2 through 45y	18 through 45y
Total in SafAS* (n)	180	1198	188
Dengvaxia	120	898	127
Control	60	300	61

<sup>16</sup> Sanofi. NS1: Risk of Symptomatic Virologically-confirmed Dengue and Dengue Hospitalization and/or Severe Dengue According to Dengue Serostatus in CYD Vaccine Efficacy Trials 125682/0

<sup>17</sup> Sanofi. NS1\_2: Risk of Symptomatic Virologically-confirmed Dengue, Dengue Hospitalization, and Severe Dengue According to Dengue Serostatus in CYD Vaccine Efficacy Trials - Extension Analysis 125682/0

Adults 18 through 45y total (n)	30	695	188
Study Location:	Vietnam	Singapore	India
Safety Results:	One death in the control group (1.7%). No related SAEs reported	No deaths. 12 (1.3%) SAEs in the Dengvaxia group and 5 (1.7%) in the control group	No deaths. 1 SAE each in the Dengvaxia (0.8%) and control (1.6%) groups

\*SafAS=Safety Analysis Set

No imbalances were noted in deaths or SAEs in any of the 3 studies.

## 4 PHARMACOVIGILANCE PLAN

### 4.1 Summary of Pharmacovigilance Plan

Sanofi has proposed a Pharmacovigilance Plan (PVP) for Dengvaxia with a safety specification to address Identified Risks, Important Potential Risks and Missing Information (Tables 6, 7 and 8 below respectively). Studies listed in the PVP are summarized in Table 9 below.

Table 6. Summary of Dengvaxia Pharmacovigilance Plan for Identified Risks<sup>18</sup>

Safety concerns	Planned Activities
Allergic /Anaphylactic Reaction	<ul style="list-style-type: none"> <li>• Routine Pharmacovigilance and TFQ for Anaphylactic Reactions</li> <li>• Study DNG15</li> </ul>
Increased risk of severe and hospitalized dengue upon vaccination in individuals not previously infected by dengue virus	<ul style="list-style-type: none"> <li>• Routine Pharmacovigilance and TFQ for Dengue Disease</li> <li>• Continue return to close monitoring of dengue cases in the Surveillance Expansion Phase for long term safety follow-up in CYD14 and CYD15. At the end of the studies, data on dengue cases in seronegative subjects from the immunogenicity subsets will be updated.</li> <li>• Final analysis by serostatus using similar methods as the NS1 Supplemental Analysis but inclusive of hospitalized and severe dengue events up to all study completion dates, and additional supplementary analysis</li> <li>• Health care provider guide with survey conducted 6 months after to evaluate effectiveness of guide</li> </ul>

TFQ=Targeted Follow-up Questionnaire

<sup>18</sup> Sanofi Pasteur. Risk Management Plan. CYD Dengue Vaccine. Version 5.0. 01Aug2018 Section 3.3 - Action Plan for Safety Issues. 125682/0

Table 7. Summary of Dengvaxia Pharmacovigilance Plan for Important Potential Risks<sup>18</sup>

Safety concerns	Planned Activities
YEL-AVD and YEL-AND	<ul style="list-style-type: none"> <li>• Routine Pharmacovigilance and TFQ for YEL-AVD, encephalitis, ADEM, and Guillain-Barré syndrome.</li> <li>• For each spontaneous report of suspected viscerotropism or neurotropism sent to the company by HCPs or a Health Authority, the company will propose specific YF 17D virus testing, if agreed by all parts.</li> <li>• Studies DNG15 and DNG11</li> </ul>
Waning protection against severe and non-severe dengue disease over time	<ul style="list-style-type: none"> <li>• Routine Pharmacovigilance and TFQ for Dengue disease</li> <li>• Long-term efficacy and safety follow-up of the 3 efficacy clinical trials (CYD14, CYD15 and CYD57)</li> <li>• Studies CYD52, CYD53, CYD69, and CYD70</li> <li>• Booster studies CYD63, CYD64 and CYD65</li> </ul>

ADEM=Acute Disseminated Encephalomyelitis, TFQ=Targeted Follow-up Questionnaire, YEL-AND=Yellow Fever (Vaccine)-Associated Neurotropic Disease, YEL-AVD=Yellow Fever (Vaccine)-Associated Viscerotropic Disease, HCPs=Healthcare Professionals

Table 8. Summary of Dengvaxia Pharmacovigilance Plan for Missing Information<sup>18</sup>

Safety Concerns	Planned Activities
Safety in immunocompromised subjects*	<ul style="list-style-type: none"> <li>• Routine Pharmacovigilance</li> <li>• Studies DNG 15 and CYD50</li> </ul>
Safety profile of inadvertent use in pregnant or lactating women	<ul style="list-style-type: none"> <li>• Routine Pharmacovigilance</li> <li>• Monitoring in clinical trials of cases of inadvertent vaccination during pregnancy</li> <li>• Studies DNG 15 and DNG16</li> </ul>
Co-administration of Dengvaxia with HPV vaccine or booster dose of Tdap vaccine	<ul style="list-style-type: none"> <li>• HPV vaccine studies CYD67 and CYD71</li> <li>• Tdap booster study CYD66</li> <li>• Inadvertent co-administration with other vaccines in DNG15</li> </ul>
Risk of severe dengue in infants born from dengue-seronegative women previously vaccinated with Dengvaxia	<ul style="list-style-type: none"> <li>• Routine Pharmacovigilance</li> </ul>

\*including subjects with congenital or acquired immune deficiency, or with HIV infection with impaired immune function, HPV=Human papillomavirus, Tdap=Tetanus-diphtheria-acellular pertussis

A total of 17 unique studies are listed in the PVP. Of the 17 studies listed in the PVP, 3 have previously been described in detail – CYD14, CYD15 (Table 3 above) and CYD57 (Table 4 above). A fourth study listed in the PVP is the Pregnancy Registry DNG16. Initially, the sponsor planned the registry in Brazil, Mexico, the Philippines and Malaysia with a goal to monitor, evaluate and assess pregnancy outcomes, and teratogenicity in children born to women exposed to Dengvaxia. The original study design included enrollment of a total of 500 women exposed to

Dengvaxia as well as 1,000 unexposed subjects across the 4 study countries or a target enrollment of 350 exposed pregnancies if the study was conducted in 2 countries. However, the sponsor has now determined that the study DNG16 is not feasible. Sanofi proposed instead “to establish a pregnancy registry to retrospectively collect data on reported exposures to Dengvaxia during pregnancy and evaluate maternal, pregnancy, birth, neonatal and infant outcomes.”<sup>19</sup> Upon further discussion with FDA, Sanofi has ultimately proposed a U.S. passive pregnancy surveillance system to “prospectively recruit women exposed to Dengvaxia during pregnancy. The registry will be designed to collect information on the baseline characteristics of the exposed women (e.g., sociodemographics, medical and obstetrical history), vaccine exposures (including Dengvaxia), pregnancy outcomes, and fetal, neonatal and infant outcomes.”<sup>20</sup> The study will be conducted as a postmarketing commitment (PMC) study and the study protocol, which will be submitted on 31Dec2019<sup>21</sup>, will be reviewed upon receipt. The remaining 13 studies listed in the PVP are described in Table 9 below. Note that these are voluntary studies, and not PMC or postmarketing requirement (PMR) studies.

**Table 9. Studies listed in the Pharmacovigilance Plan for Dengvaxia**

<b>Study title location &amp; type</b>	<b>Objectives</b>	<b>Safety concerns addressed</b>	<b>Status &amp; final report submission date</b>
DNG11 (Mexico, Brazil and Malaysia): Incidence study	To assess the background incidence of Neurotropic and Viscerotropic-Like Diseases before Dengvaxia introduction.	YEL-AVD and YEL-AND	Complete 6 Dec 2017
DNG15 (Brazil, Mexico, Philippines, Malaysia): Cohort Event Monitoring study	To evaluate the safety profile of Dengvaxia in the real-world immunization setting. To describe, demographic and comorbid conditions in the population vaccinated with Dengvaxia.	Safety Exposures in pregnancy, Allergy or anaphylaxis, Viscerotropic and neurotropic diseases	Ongoing 31 Dec 2025
(b) (4)	(b) (4)	(b) (4)	(b) (4)
CYD63 (Singapore), CYD64 (Brazil, Colombia, Honduras, Mexico, Puerto Rico), & CYD65 (Colombia, Philippines): Booster studies	To evaluate the safety and immunogenicity of a booster dose administered 4-5 years after the third dose (CYD63 and CYD64). To evaluate the safety and immunogenicity of 1-, 2-, or 3-Dose Schedules Followed by a Single Booster (CYD65).	Waning of protection over time Need for booster	Ongoing 31 Dec 2019 for CYD63 and CYD64 31 Mar 2021 for CYD65
CYD50 (Brazil): Exposure in HIV+ adults	To evaluate immunogenicity and safety in clinically stable HIV+ adults on antiretroviral therapy.	Exposure in immunocompromised population	Planned 30 Jun 2022

<sup>19</sup> Sanofi. Safety Information Amendment. 22Apr2019 125682/0.47

<sup>20</sup> Sanofi. Safety Information Amendment. 22Apr2019 125682/0.52

<sup>21</sup> Sanofi. Safety Information Amendment. 29Apr2019 125682/0.54

CYD66 (Philippines), CYD67 (Malaysia), and CYD71 (Mexico): Co-administration studies	The studies evaluate the safety and immunogenicity of co-administration of CYD dengue vaccine with other vaccines: booster dose of Tdap (CYD66), HPV Vaccine (CYD67 and CYD71).	Co-administration with Tdap, HPV vaccines	Ongoing 31 Dec 2020
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YEL-AND=Yellow Fever (Vaccine)-Associated Neurotropic Disease, YEL-AVD=Yellow Fever (Vaccine)-Associated Viscerotropic Disease

## **4.2 Reviewer Assessment of the Pharmacovigilance Plan**

### **4.2.1 Strengths and Limitations of the Clinical Safety Database**

The safety specification in the sponsor's Pharmacovigilance Plan lists safety concerns derived from Sanofi's clinical trial experience with Dengvaxia. Strengths of the clinical safety database include multiple randomized controlled trials, long term follow up of study subjects and a large overall trial population in excess of 30,000 subjects (section 3 above).

There are however, several limitations of the clinical safety database. Long-term follow-up from the Phase 3 trials, CYD14 and CYD15 is planned postmarketing (Table 6). However, all study subjects did not undergo pre-vaccination screening, and most are from outside the U.S. A relatively small number of study subjects in Puerto Rico are included in the clinical safety database (Table 3). Given geographic variations in local dengue disease epidemiology, extrapolation from the larger overall safety database to populations in U.S. regions endemic for dengue is challenging. While the clinical safety database reviewed is large (section 3 above), adults represent less than 3% of subjects (Table 5 above). However, given Sanofi's recent decision to pursue licensure only in individuals aged 9 through 16 (section 2.3.1), the adequacy of safety data in adults is less germane to the current age indication. With regard to safety in the younger population, since seroprevalence can vary with age - with lower seropositivity at younger ages - the performance of the test used to identify potential seropositive vaccinees continues to be of particular importance in this younger age group. And, of note, although Sanofi's NS1 Supplemental Study to evaluate the safety signal for hospitalized/severe dengue in young children was reassuring, the sponsor's evaluation was a post-hoc analysis with unexpected results from the initial study, requiring an extension and additional study modifications (section 3.1.3).

### **4.2.2 Adequacy of the Pharmacovigilance Plan**

Sanofi's proposed Pharmacovigilance Plan for Dengvaxia is adequate for the labeled indication.

As part of the assessment of the adequacy of the PVP, given the safety signal identified in CYD14 and the findings of the NS1 supplemental study (section 3.1.3), particular attention was paid to the risk of severe dengue in seronegative vaccinees. Should the product be approved, the sponsor's planned activities to avoid inadvertent vaccination of seronegative individuals include routine pharmacovigilance with targeted follow-up of cases identified through spontaneous reporting as well as an education guide for healthcare providers (Table 6). Sanofi indicates that the targeted follow up questionnaire will "assist with case classification with regards to the level of diagnostic certainty and disease severity, and ultimately, contribute to signal detection

activities.”<sup>22</sup> Of note, the education guide is not part of a Risk Evaluation and Mitigation Strategy (REMS) program and is therefore not implemented as an FDA-required activity.

The feasibility of additional pharmacovigilance activities, such as a REMS, to address the safety concern regarding the increased risk of hospitalized/severe dengue in seronegatives has been explored at length. “FDA can require a REMS before initial approval of a new drug application ... to ensure that the benefits of the drug outweigh its risks, after the drug has been approved.”<sup>23</sup> Because the benefits of the vaccine as currently indicated and labeled are expected to outweigh the risks, a REMS is not required at this time. The current labeled indication is for individuals with “laboratory-confirmed previous dengue infection” and the *Limitations of use* section of the label notes that “Those not previously infected are at increased risk for severe dengue disease when vaccinated and subsequently infected with dengue virus.” Additionally, the *Warnings and Precautions* section of the label notes that: “Healthcare professionals must evaluate individuals for prior dengue infection to avoid vaccinating individuals who have not been previously infected by dengue virus... Available tests may vary in specificity (e.g., false positivity due to cross-reactivity with other flaviviruses).”<sup>24</sup>

Upon further discussion, Sanofi has also submitted a proposal for strategies to support the appropriate use of Dengvaxia according to the label.<sup>24</sup> Sanofi’s proposal includes exploring potential collaboration with existing dengue surveillance systems in Puerto Rico. Dengue fever and dengue hemorrhagic fever are reportable diseases by law in Puerto Rico.<sup>25</sup> The island-wide, laboratory-based Passive Dengue Surveillance System (PDSS) has been conducted in Puerto Rico for more than 30 years by the CDC’s Dengue Branch and the Puerto Rico Department of Health (PRDH). The PDSS provides a mechanism for healthcare providers to initiate requests for diagnostic testing and submit serum samples from suspected dengue case-patients. The specimens are processed by PRDH free of charge and test results are sent to the submitting provider. Patient demographic and clinical information are entered into an electronic data system. The PRDH also manages the Puerto Rico Immunization Registry (PRIR) a web-based database that records and tracks demographic and immunization information for vaccinees island-wide.<sup>26</sup>

Sanofi proposes providing support to the PRDH to adapt the existing PRIR to record pre-vaccination serostatus and prompt providers whether or not to offer vaccination to a given individual.<sup>23</sup> Sanofi notes that discussions with the PRDH indicate that “these adaptations are feasible provided that corresponding public funding is approved and that their implementation may potentially occur between summer 2020 and first quarter 2021.”<sup>22</sup> The sponsor also plans to “enter into discussions with the [PRDH] and the CDC about the possibility of sharing dengue surveillance data.”<sup>21</sup>

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<sup>22</sup> Sanofi. Safety Information Amendment. 8Apr2019 125682/0.41

<sup>23</sup> FDA. FDA’s Application of Statutory Factors in Determining When a REMS Is Necessary. Guidance for Industry. April 2019

<sup>24</sup> Sanofi. Proposed strategies to support the appropriate use of Dengvaxia according to the label 11Apr2019 125682/0.43

<sup>25</sup> CDC. Dengue in Puerto Rico. <https://www.cdc.gov/dengue/about/inpuerto.html> Accessed 12Apr2019

<sup>26</sup> Puerto Rico Immunization Registry. Available at <https://prir.salud.gov.pr/PRIRPRD/portalHeader.do> Accessed 16Apr2019

A future postmarketing study may help quantify the risk in the U.S. population, by determining the incidence of severe dengue in vaccinees and evaluating the performance of available tests, particularly if a point-of-care, rapid diagnostic high-performing test becomes available for comparison to available testing modalities. Due to the relative rarity of severe dengue, sample size calculations indicate that a large number of study subjects would be required for such a study to provide meaningful results. For instance, in the absence of a dengue outbreak in Puerto Rico, it is estimated that a total of 10,000 vaccinees over a 5 year period would be required in order to observe 4 cases of severe/hospitalized dengue, or 1 case specifically from a vaccinee who tested false positive (Appendix). Currently, the large sample size precludes a traditional study and FDA's Sentinel system has limited representation in U.S. areas where dengue is endemic.

Continued assessment and monitoring will be important as severe/hospitalized dengue continues to be a risk in individuals who are not appropriately screened as per the label, or who are screened but incorrectly classified as seropositive (i.e., false positives).

## **5. RECOMMENDATION**

Should the product be approved, OBE/DE finds the proposed Pharmacovigilance Plan for Dengvaxia (Risk Management Plan, version 5.0, dated August 1, 2018) submitted under original BLA 125682/0 to be adequate for the labeled indication. OBE/DE agrees with spontaneous reporting with a targeted follow-up questionnaire, limiting use to individuals screened for seropositivity, labeling of the risk of severe/hospitalized dengue, and other pharmacovigilance activities as described above. We recommend that the international postmarketing experience with severe dengue including hospitalization and death (section 2.4.1) be included in section 6.2 *Postmarketing Experience* section of the package insert. OBE/DE notes the criticality of pre-vaccination serostatus assessments since the use of Dengvaxia is contingent upon a screen-and-vaccinate approach, and (b) (4)

## **APPENDIX**