Vaccines and Related Biological Products Advisory Committee Meeting
March 7, 2019

FDA Briefing Document

Dengue Tetravalent Vaccine, Live

(Proposed Trade Name: Dengvaxia)

Applicant:
Sanofi Pasteur, Inc.

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Glossary

BLA	Biologics License Application
CI	Confidence interval
CYD	Chimeric yellow fever dengue
DHF	Dengue hemorrhagic fever
DSS	Dengue shock syndrome
FDA	Food and Drug Administration
GCP	Good clinical practice
IDMC	Independent data monitoring committee
LB	Lower bound
NS1	Non-structural protein 1
PPSE	Per protocol analysis set for efficacy
SAE	Serious adverse event
SEP	Surveillance expansion period
VCD	Virologically-confirmed dengue
VE	Vaccine efficacy
WHO	World Health Organization

1.0 Executive Summary

A biologics license application (BLA) was submitted by Sanofi Pasteur, Inc. to the US Food and Drug Administration (FDA) for a live, quadrivalent dengue virus vaccine (the proposed trade name Dengvaxia will be used in this briefing document). The candidate vaccine contains the replication genes and the capsid gene from the attenuated Yellow Fever [17D] virus, and the Pre-M and ENV genes from each of the four dengue serotypes. The proposed indication is "for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in individuals 9 through 45 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 current serotesting."

The BLA includes efficacy, immunogenicity, and safety data from 16 studies, including two phase 3 and one phase 2b clinical endpoint efficacy studies (CYD15, CYD14, and CYD23, respectively), three immunogenicity and safety studies submitted to support use of Dengvaxia in adults ages 18 - 45 years (CYD47, CYD28, and CYD22) and one study to support manufacturing consistency (CYD17). The 9 additional studies submitted were small, early-phase, safety and immunogenicity studies, and as such, the data are not reviewed in the briefing document.

CYD15 was a randomized, placebo-controlled, observer-blind, multicenter study that evaluated vaccine efficacy (VE), immunogenicity and safety of Dengvaxia in subjects ages 9 – 16 years. Subjects at sites in Puerto Rico, Central America and South America were randomly allocated in a 2:1 ratio to receive 3 doses of Dengvaxia (N = 13,920) or normal saline placebo (N = 6,949) at day 0, month 6 and month 12. The primary efficacy endpoint was absolute VE against symptomatic virologically-confirmed dengue (VCD) starting at >28 days after receipt of the final month-12 vaccination until month 25. For study CYD15, the primary efficacy success criterion

was met if the lower bound (LB) of the 95% confidence interval (CI) was >25%. The primary efficacy criterion was met with an estimated VE of 60.8% (95%CI: 52.0, 68.0).

Regarding solicited adverse reactions, pain was the most frequent injection site reaction reported within 7 days after each injection, with 32.4% and 26.3% of subjects in the Dengvaxia and placebo groups, respectively, reporting injection site pain after the first injection. The percentage of subjects reporting pain was lower after subsequent injections in both groups (table 8). Most reactions were mild or moderate (grade 1 or grade 2) and rates of severe reactions were balanced between groups. Headache was the solicited systemic reaction most frequently reported within 14 days after each injection (39.9% and 41.6% of subjects in the Dengvaxia and placebo groups, respectively, after the first injection) (table 9). The percentage of subjects reporting headache was lower after subsequent injections in both groups. Both treatment groups showed similar rates of malaise, myalgia or asthenia after the first injection (around 25% - 30%), the frequency of which decreased after subsequent injections and remained balanced. The majority of reactions were reported as mild to moderate (grade 1 or grade 2). Unsolicited adverse events within 28 days of vaccination were balanced across groups with regard to frequency and nature and were representative of common conditions seen in childhood (e.g., upper respiratory tract infections, otitis media, asthma, diarrheal illness).

Study CYD14 was identical to CYD15 in study design regarding important features including: the primary efficacy objective, endpoint and success criterion, safety evaluations, duration of follow-up for the active phase, and definitions of the statistical analysis sets. The key differences were that subjects were ages 2 - 14 years and were from Southeast Asian/Pacific Islands sites (N = 10,275, with 6,851 and 3,424 in Dengvaxia and placebo groups, respectively). For study CYD14 the primary efficacy success criterion was met with an estimated VE of 56.5% (95%CI: 43.8, 66.4).

CYD23 was the third efficacy study and was similar in design to that of CYD15 and CYD14, although it was a smaller phase 2b study conducted at a single site in Thailand in children ages 4 -11 years (N = 4,002 with 2,669 and 1,333 in the Dengvaxia and placebo groups, respectively). The study did not meet the prespecified primary efficacy criterion with an estimated VE of 30.2% (95%CI: -13.4, 56.6). During the 25-months active phase, safety concerns were not identified and safety results were similar to that of CYD15.

Studies CYD47, CYD28, and CYD22 submitted to support use in adults ages 18 - 45 years were randomized, observer-blind, placebo and/or active-controlled studies from which descriptive safety and immunogenicity data were obtained. Serotype-specific GMTs were compared to those of dengue immune adolescents in the immunogenicity subsets from the efficacy studies (approximately 10% of subjects in CYD15 and 20% of subjects in CYD14). Descriptively, in studies CYD22 and CYD47 where dengue endemicity was established, post-dose 3 GMTs among vaccinated dengue-immune adults ages 18-45 years of age were similar to post-dose 3 GMTs of dengue-immune vaccinated subjects ages 9-16 years in the immunogenicity subsets from efficacy studies CYD14 and CYD15 that were also conducted in dengue-endemic regions.

To evaluate for rare, unanticipated adverse reactions, the data from all subjects 9 to 45 years of age who received the final formulation/dose were pooled for additional analyses. This dataset included safety outcomes for 20,426 subjects up to at least 6 months after each dose. Within the 6 months post-dose time frame, the pattern and rates of SAEs were unremarkable for this subject population and were similar for the Dengvaxia and placebo arms.

In the initial analyses of long term follow-up data, i.e., through 60 months post-dose 1, a safety signal became apparent for increased risk of severe dengue in the younger cohorts of Dengvaxia recipients, particularly in subjects 2 to 5 years of age. To investigate this signal, the sponsor performed additional laboratory testing and re-analyzed the long-term follow-up data on severe/hospitalized VCD from the efficacy studies CYD14, CYD15, and CYD23. Although age could not be ruled out as a contributing factor, the primary variable associated with increased relative risk of hospitalized VCD in Dengvaxia recipients was dengue non-immune status at baseline. Based on these analyses, the sponsor is requesting approval for use only for individuals 9 through 45 years of age with laboratory-confirmed previous dengue infection and living in endemic areas.

The applicant has proposed both routine and enhanced pharmacovigilance monitoring to identify risks that could be associated with Dengvaxia, including allergic reactions, severe and hospitalized dengue in individuals not previously infected by dengue virus, as well as risks that have not been previously recognized.

This Vaccines and Related Biological Products Advisory Committee **(**VRBPAC) meeting is being convened to review and discuss the efficacy, immunogenicity, and safety data derived from trials conducted with Dengvaxia and submitted in the BLA.

2.0 Background

2.1 General Product Information

Product name:	Proper name: Dengue Tetravalent Vaccine, Live
Proposed trade name:	Dengvaxia®
Product description:	Dengvaxia is a live, attenuated, tetravalent, chimeric virus vaccine, containing the replication genes and the capsid gene from the attenuated Yellow Fever [17D] virus, and the Pre-M and ENV genes from each of the four dengue serotypes (CYD). Each CYD virus is purified from Vero cells.
Proposed Indication:	Dengvaxia is a vaccine indicated for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in individuals 9 through 45 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 current serotesting.
Dosage and Administration:	Dengvaxia is supplied as a vial of lyophilized powder containing each of the four CYD virus components that is reconstituted at the time of use with the supplied diluent (0.4% NaCl). After reconstitution, each 0.5-mL dose of Dengvaxia is formulated to contain 4.5 - 6.0 $\log_{10}$ $CCID_{50}$ of each of the CYD virus components. The reconstituted vaccine is administered

subcutaneously in three doses at 6-month intervals (at day 0, month 6, and month 12).

2.2 Epidemiology

Dengue infection is caused by dengue virus which includes 4 known serotypes (dengue virus 1, 2, 3, and 4), all transmitted primarily by *Aedes aegypti* mosquitos, as well as other members of the *Aedes mosquito* family. Annually, an estimated 390 million dengue infections occur worldwide, of which approximately 100 million are associated with clinical manifestations; 500,000 with hospitalization; and 20,000 with death [1].

Dengue disease is a major public health concern in more than 128 countries. It is endemic in Asia, the Pacific area, Africa, and Latin America (including the Caribbean), with the four dengue virus serotypes found in tropical and sub-tropical regions, including some European territories [2]. Dengue is endemic in Puerto Rico[4], Guam, Samoa, and the U.S. Virgin Islands. After decades of absence in the continental U.S., locally acquired cases have emerged at the Texas-Mexico border as well as in Hawaii.

2.3 Clinical Manifestations, Diagnosis, Treatment, and Prevention

The clinical manifestations of dengue infection range from asymptomatic, to a non-specific, self-resolving, acute febrile illness often associated with chills, headache, retro-orbital pain, myalgia, arthralgia, rash, hemorrhagic manifestations, and/or leucopenia, to severe and life-threatening. Severe dengue disease (e.g., dengue hemorrhagic fever [DHF]) is classified by the WHO into four grades of severity and represents approximately 5-10% of all clinically apparent dengue infections. Less than 1% of patients develop grade III and IV DHF (also termed DHF/DSS [dengue shock syndrome]), defined by one or more of the following: (i) plasma leakage that may lead to shock and/or fluid accumulation (DSS), and/or (ii) severe bleeding, and/or (iii) severe organ impairment (liver, CNS, heart) [5]. Of note, children with severe dengue are particularly susceptible to shock, with the highest mortality in infants.

Severe dengue disease is not associated with a particular dengue serotype, and natural infection with any serotype typically results in lifetime protection from that serotype [5]. However, a person is susceptible to infections from the other three dengue serotypes after his/her first dengue infection. Approximately 95% of all cases of severe/hospitalized dengue are observed in the context of second heterologous infections.

Laboratory confirmation of dengue infection of individuals with compatible clinical symptoms can include direct detection methods (viral culture, reverse transcriptase polymerase chain reaction, or nonstructural protein 1 immunoassay) or indirect methods (single IgM ELISA or paired acute and convalescent IgM or IgG ELISAs). The reliability of serologic tests can be impacted by prior dengue infection and cross-reactivity to co-circulating flaviviruses (e.g., Zika). No serologic tests are cleared by FDA to establish prior exposure to dengue. Currently available IgG ELISAs may lead to false positive results because of low specificity and thus, the potential for detecting cross-reactive antibodies to other flaviviruses.

In the U.S., there are no approved vaccines or antiviral treatments for dengue. Treatment of dengue disease is supportive, with rest, control of fever and pain with antipyretics/ analgesics, and adequate fluid intake. Supportive intensive care and fluid management are the mainstays of therapy for severe disease. Preventive measures include mosquito vector control and personal protection measures.

3.0 Overview of Clinical Studies

Sixteen clinical studies, were submitted to the Biologics License Application (BLA). The data from seven phase 3 and phase 2 studies intended to support use in children and adults ages 9 - 45 years are summarized in Table 1 and will be discussed in Sections 4, 5, and 6 of this document as follows:

- Section 4: Studies Supporting Efficacy will describe study designs, patient population, efficacy results and selected safety results [local and systemic reactogenicity and unsolicited adverse events (AEs)] for studies CYD15, CYD14, and CYD23 for data accrued during the active phase of the study (i.e., the timepoint at which the primary efficacy endpoint was evaluated; 25 months from first vaccination).
- Section 5: Immunogenicity Data Supporting Use in Adults Ages 18-45 Years will present an overview of study designs and descriptive immunogenicity data from studies CYD 47, 28, and 22 (and reference immunogenicity data from the clinical endpoint efficacy studies described in Section 4 (CYD15, CYD14, CYD23).
- Section 6: Integrated Summary of Safety will discuss serious adverse events (SAEs), severe dengue disease, and vaccine viremia, and shedding.

Study CYD17, intended to support manufacturing consistency and conducted in Australia, will not be discussed beyond Table 1 because the study met predefined study success criteria for similar immune responses across lots for post-dose 3 geometric mean titers (GMTs) against the four parental serotypes, and the safety results (i.e., local and systemic reactogenicity) were generally consistent with the aforementioned studies. The remaining 9 studies submitted to the BLA will not be discussed further as they were small safety and immunogenicity studies conducted in the early phase of development, the results of which were generally deemed consistent with the studies described in the briefing document.

Table 1. Overview of Selected Clinical Studies Submitted to the Dengvaxia BLA STN 125682/0

Study Number	Study Design (Phase)	Main Objectives	Sample size and dosing regimen	Age range	Countries (endemicity)
CYD15	Randomized 2:1, placebo- controlled, observer-blind, multi-center (phase 3)	**- VE against VCD** - Immunogenicity - Safety	N[1] = 20,869 Dengvaxia (n[2]= 13,920) or placebo (n = 6,949)[3]	9-16 years	Brazil, Colombia, Honduras, Mexico, Puerto Rico (dengue - endemic)
CYD14	Identical to CYD15 (phase 3)	Identical to CYD15	N = 10,275 Dengvaxia (n = 6,851) or placebo (n = 3,424)	2-14 years	Indonesia, Malaysia, Thailand, the Philippines, Viet Nam (dengue - endemic)
CYD23	Similar to CYD15 - differences highlighted where important (phase IIb)	Similar to CYD15 – differences highlighted where important	N = 4,002 Dengvaxia (n = 2,669) or placebo (n = 1,333)	4-11 years	Thailand (dengue - endemic)
CYD57	Extension study to CYD23 for hospitalization for dengue and severe dengue disease	Safety	N = 3,203 Dengvaxia (n = 2,131) or placebo (n = 1,072)	4-11 years at time of enrollment to CYD23	Thailand (dengue-endemic)

Study Number	Study Design (Phase)	Main Objectives	Sample size and dosing regimen	Age range	Countries (endemicity)
CYD47	Randomized (2:1), placebo-controlled, observer-blind, multi-center (phase II)	Descriptive immunogenicity (intended to support immune bridging from children to adults ages 18-45 years)	N = 189 Dengvaxia (n = 128) or placebo (n = 61)	18-45 years	India (dengue-endemic)
CYD28	Randomized (3:1), placebo-controlled, observer-blind, single-center (phase II)	Identical to CYD47 (intended to support immune bridging from children to adults ages 18-45 years)	N = 1,198 Dengvaxia (n = 898 [521 adults ages 18-45 years; 377 adolescents and children ages 2-17 years]) Control[4] (n = 300 [174 adults; 126 adolescents and children])	2-45 years	Singapore (dengue-endemic)
CYD22	Randomized (2:1), placebo-controlled, observer-blind, single-center (phase II)	Identical to CYD47 (intended to support immune bridging from children to adults ages 18-45 years)	N = 180 Dengvaxia (n = 120 [20 adults; 100 adolescents and children ages 2 -17 years]) Control[5]: (n = 60 [10 adults; 50 adolescents and children])	2-45 years	Vietnam (dengue-endemic)

Source: Adapted from STN 125682/0, Tabular Listing of Clinical Studies

[1]N: number per treatment group who were enrolled and randomized.

[2]n: per treatment group

[3]Unless otherwise specified vaccine regimens were administered at Day 0, month 6, and month 12

[4] For control groups: If < 12 years Placebo (NaCl 0.9%) at D0. Hepatitis A vaccine (Havrix®) at M6 and M12. If ≥ 12 years Placebo (NaCl .9%) at D0. Influenza vaccine (Vaxigrip®) at M6 and M12.

[5] For control groups: Meningococcal Polysaccharide A+C vaccine at D0; placebo at month 6; Typhoid Vi Polysaccharide vaccine (Typhim Vi®) at month 12.

4.0 Studies Intended to Support Efficacy (CYD15, CYD14, CYD23)

As outlined in table 1, the study designs of CYD15, CYD14, and CYD23 were identical in most respects (i.e., primary efficacy objective, endpoint and success criterion; safety evaluations, duration of follow-up for the active phase, definitions of the statistical analysis sets discussed in this briefing document). The largest study, CYD15, will be described in the most detail. For the subsequent studies, CYD14 and CYD23, key areas of divergence from CYD15 study design (e.g., demographics, study site regions) will be highlighted to support discussion of the efficacy and safety data accrued during the active phase of each study (figure 1).

4.1 Study CYD15

4.1.1 CYD15 Study Design

Study CYD15 Title:
Efficacy and Safety of a Novel Tetravalent Dengue Vaccine in Healthy Children and Adolescents Aged 9 to 16 Years in Latin America

Study CYD15 Design:
This was a randomized, placebo-controlled, observer-blind, multi-center study conducted at 22 sites across Brazil, Colombia, Honduras, Mexico, and Puerto Rico. Healthy children and adolescents ages 9-16 years were randomized 2:1 (Dengvaxia: placebo) and stratified (ages 9-11 and 12-16 years) to receive Dengvaxia or placebo at day 0, month 6 and month 12. For all subjects, SAEs were followed for the entire 6-year study duration. Subjects recruited during the first 2 months were randomized to the reactogenicity and immunogenicity subset until 2,000 subjects had been enrolled. For this subset, injection site reactions, systemic reactogenicity, and unsolicited AEs were collected via diary card for 7, 14, and 28 days post-each vaccination, respectively; and blood for immunogenicity was obtained before and at 28 days after each vaccination. Follow-up for all study participants was broken up into three phases described below in text and figure 1.

Active Phase: The Active Phase began at Day 0, first vaccination, and continued through 13 months after the last dose was administered (Month 25). During this phase, active surveillance for symptomatic virologically-confirmed dengue (VCD) was conducted via at least weekly contact with parents/guardians of the study subjects by phone calls, SMS texts and/or home visits to identify cases of acute febrile illness and test for dengue infection as soon as possible or within 5 days of fever onset. Parents were also instructed to directly contact the study team for episodes of febrile illness.

Hospitalization Phase: The Hospitalization Phase intended to assess vaccine safety related to hospitalization for VCD started at the end of the Active Phase (Month 25) and continued for 3 years. During the hospitalization phase, parents/guardians of study subjects were contacted every 3 months and surveillance of non-study healthcare sites and school absenteeism was performed. Subjects with a febrile illness requiring hospitalization were screened for dengue infection by serum RT-PCR or Non-structural protein 1 (NS1) antigen testing. During the second year of the hospital phase, subjects had the option to reconsent to participate in the surveillance expansion period (SEP) which reinitiated the active surveillance procedures performed during of the Active Phase. Those who did not consent continued on with Hospitalization Phase surveillance procedures.

SEP: Upon reconsenting to participate in the SEP, a serum sample was obtained and subjects underwent active surveillance procedures for dengue disease as performed during the active phase. The goal of the SEP was to detect VCD cases (hospitalized or not) and to describe VE and vaccine safety related to hospitalized VCD. The complete data are not yet available and per agreements reached with FDA will be submitted formally post-licensure (see Section 6 Integrated Summary of Safety for further discussion).

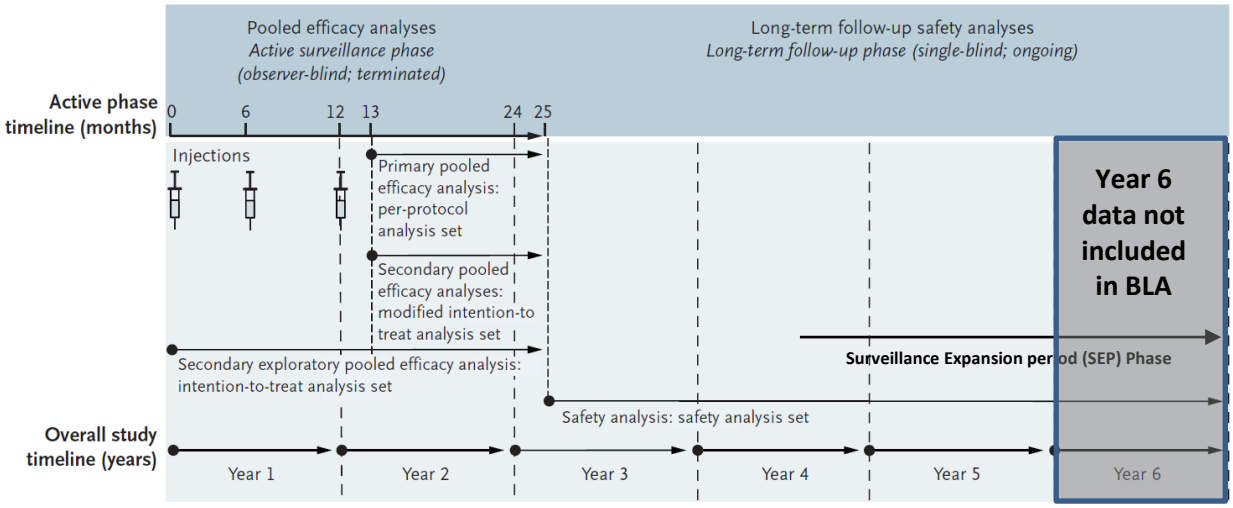


Figure 1: Overview of the Surveillance Phase and Long-Term Follow-up Phase for CYD 14, CYD 15 and CYD 23/57. Adapted from Hadinegoro et al. (2015) NEJM v273(13), p1195-1206.

Case definition:

Virologically-Confirmed Dengue Cases:

VCD was defined as an acute febrile illness (i.e., temperature ≥ 38°C on at least 2 consecutive days) virologically-confirmed by dengue RT-PCR (both screening and serotype specific assays) and/or dengue NS1 ELISA Ag test.

Severe Dengue Cases:

- Platelet count ⩽ 100 000/μL and bleeding (tourniquet, petechiae or any bleeding) plus plasma leakage (effusion on CXR or clinically apparent ascites including imaging procedures or hematocrit ⩾ 20% above baseline recovery level or standard for age if only one reading).
- Shock (pulse pressure ⩽ 20 mmHg in a child, or hypotension [⩽ 90 mmHg] with tachycardia, weak pulse and poor perfusion)
- Bleeding requiring blood transfusion
- Encephalopathy (unconsciousness or poor conscious state or convulsions not attributable to simple febrile convulsion, as defined in the guidelines for definition and collection of febrile convulsions, or focal neurological signs). Poor conscious state or unconsciousness must be supported by Glasgow Coma Scale (GCS) or Blantyre Coma Score.
- Liver impairment (AST > 1000 IU/L or prothrombin time [PT] International normalized ratio [INR] > 1.5) excluding other causes of viral hepatitis.
- Impaired kidney function (Serum creatinine ⩾ 1.5 mg/dL) not due to other cause.

Dengue Hemorrhagic Fever (DHF) Cases:

The definition of DHF Grade I, II, III, and IV is consistent with the 1997 WHO definition:

- Clinical manifestations:
  - Fever: acute onset, high (≥ 38°C) and continuous, lasting 2 to 7 days
  - Any of the following hemorrhagic manifestations: a positive tourniquet test, petechiae, purpura, ecchymosis, epistaxis, gum bleeding, and

hematemesis and/or melena

- Laboratory Findings
  - Thrombocytopenia (platelet count ≤ 100,000/μL)
  - Plasma leakage as shown by hemoconcentration, pleural effusion, ascites and/or hypoalbuminemia

The first two clinical criteria, plus thrombocytopenia and signs of plasma leakage are sufficient to establish a clinical diagnosis of DHF.

DHF is graded as follows:
Grade I: Fever and constitutional symptoms; the only hemorrhagic manifestation is a positive tourniquet test.
Grade II: Grade I manifestations along with another form of spontaneous bleeding
Grade III: Clinically apparent hypotension
Grade IV: Profound shock with undetectable blood pressure and pulse

Study CYD15 Objectives and Endpoints:
Primary Objective: To assess the efficacy of 3 doses of Dengvaxia administered at 0, 6 and 12 months to prevent symptomatic VCD cases, regardless of the severity, due to any of the four serotypes.

Primary Endpoint: symptomatic, VCD cases occurring > 28 days after Dose 3 (i.e., month 13 through month 25 of Active Phase). Success criteria for the endpoint was defined as a the lower bound (LB) of the 95%CI of VE > 25%.

Descriptive Secondary Objectives and Endpoints:
Occurrence of dengue cases was evaluated for the whole Active Phase (including 28 days post first vaccination). VE by serotype was assessed. Occurrence of severe dengue disease (hospitalization, DHF and DSS) was evaluated during all study phases (figure 1).

Safety Objectives and Endpoints:
To describe SAEs in all subjects over the entire study period. To describe injection site, systemic reactogenicity, and unsolicited AEs for 7, 14, and 28 days post-vaccination, respectively, in the immunogenicity and safety subset.

Study CYD15 Eligibility:
Healthy, consented/assented, children and adolescents ages 9 -16 years were enrolled.

Selected Analysis Populations:
Per Protocol Analysis Set for Efficacy (PPSE):
The primary efficacy analysis was evaluated in the PPSE. Subjects in this group received all three doses of vaccine for which they were randomized to receive within the pre-specified time frame, had acceptable follow-up through the end of the active phase, and complied with major elements of good clinical practice (GCP) and study surveillance procedures.

Safety Analysis Set (SAS):
Safety analyses were evaluated in the SAS which included all subjects who received at least one dose of vaccine and complied with major elements of GCP.

Full Analysis Set for Efficacy (FASE):
Secondary analyses were conducted on the FASE. The FASE included all subjects who received at least one injection regardless of the per-protocol criteria and who did not have serious non-compliance to GCP.

Full Analysis Set for Immunogenicity (FASI) and Reactogenicity Analysis Set:
The immunogenicity and reactogenicity analyses were conducted on subjects included in the immunogenicity and reactogenicity subset (N=2000) who received at least one injection, who had a blood sample drawn and a result available after this injection and who did not have serious non-compliance to GCP.

4.1.2 Study CYD15 Results

Study CYD15 Trial Population:
Table 2 shows subject disposition and analysis groups that were used to evaluate the primary efficacy endpoint (PPSE) and safety endpoints (SAS and reactogenicity subset). Most patients who withdrew (4.5%) did so voluntarily and not related to an AE (3.5%) or were noncompliant with procedures or lost to follow-up (0.3% and 0.7% respectively). Eleven subjects (7 [0.1%] and 4 [0.1%], in Dengvaxia and placebo groups, respectively) did not complete the study due to an SAE.

Subjects were excluded from the per protocol efficacy and per protocol immunogenicity analysis sets (PPSE, and PPSI, respectively) largely because they either did not receive all three vaccinations or did not receive them within the pre-specified time-frame. The immunogenicity analyses will be discussed in Section 5 Immunogenicity Data Supporting Use in Adults Ages 18 - 45.

Table 2. Analysis Groups for Subjects Enrolled to Study CYD15

Treatment Group	Dengvaxia n[1] (%)	Placebo n (%)	Total n (%)
Enrolled and randomized	13,920 (100)	6,949 (100)	20,869 (100)
Completed active phase	13,281 (95.4)	6,640 (95.6)	19,921 (95.5)
PPSE[2]	12,573 (90.3)	6,261 (90.1)	18,834 (90.2)
SAS[3]	13,915 (100)	6,939 (100)	20,854 (100)
Reactogenicity analysis set	1,333 (100)	664 (100)	1,997 (100)
Full analysis set for immunogenicity	1,301 (97.5)	643 (96.5)	1,944 (97.2)

Source: Adapted from STN 125682/0 Clinical Study Report for CYD15 tables 4.2, 4.7, 4.8, and 4.10
[1]n = number per specified category in table
[2]PPSE = Per-Protocol Analysis Set for Efficacy
[3]SAS = Safety analysis set

Table 3 shows that subject age and sex were balanced across treatment groups. Nearly all (99.9%) of subjects identified as Hispanic or Latino, consistent with the region from which they were enrolled (Puerto Rico, Central America, South America).

Table 3. Demographics for Subjects Enrolled to Study CYD15 (SAS[1])

Treatment Group	Dengvaxia N[2] = 13,915	Placebo N = 6,939	Total N = 20,854
Male, n[3] (%)	6,875 (49.4)	3,409 (49.1)	10,284 (49.3)
Female, n (%)	7,040 (50.6)	3,530 (50.9)	10,570 (50.7)
Mean age in years (standard deviation)	12.5 (2.14)	12.5 (2.13)	12.5 (2.14)

Source: Adapted from STN 125682/0 Clinical Study Report for CYD15 table 10.22
[1]SAS = Safety analysis set
[2]N = Total safety analysis set for by treatment group and total
[3]n = number per specified category in table

Study CYD15 Primary Efficacy Results
The primary efficacy endpoint was symptomatic VCD due to any of the 4 serotypes occurring >28 days after the 3rd vaccination for 12 months. As shown in table 4, the prespecified success criterion for VE (LB of the 95%CI >25%) was met (60.8% [95%CI: 52.0, 68.0]).

Table 4. Vaccine Efficacy Against Symptomatic Virologically-Confirmed Dengue Post-Dose 3 During Active Phase Due to Any of the 4 Serotypes for Study CYD15 (PPSE[1])

Treatment group	Cases[2]	Number of episodes	Person-years at risk	Density Incidence (95% CI)	%VE[3] (95% CI)
Dengvaxia N[4] = 12,573	176	176	11,792	1.5 (1.3, 1.7)	**60.8 (52.0, 68.0)**
Placebo N = 6,261	221	221	5,809	3.8 (3.3, 4.3)	--

Source: Adapted from STN 125682/0 Clinical Study Report for CYD15 table 5.1
[1]PPSE = Per-protocol analysis set for efficacy
[2]Cases: number of subjects with at least one symptomatic virologically-confirmed dengue episode from 28 days post-injection 3 to the end of Active Phase.
[3]VE = Vaccine efficacy, success criterion was met if the LB of the of the 95%CI for VE was >25%
[4]N = Number in treatment group, PPSE

Study CYD15 Additional Descriptive Analyses During Active Phase of Study:
Evaluation of VE during the active phase against any strain occurring any time after the first dose was consistent with the analysis of the primary endpoint, with an estimated VE of 64.7% (95%CI: 58.7, 69.8) (table 5). In this descriptive secondary analysis, it is notable that numerically, although VE is observed for all serotypes, VE is generally higher for serotypes 3 and 4, and lower for serotype 2 in each of the clinical efficacy endpoint trials.

Table 5. Vaccine Efficacy Against Symptomatic Virologically-Confirmed Dengue During the Active Phase Any Time Post Dose 1 Due to Each Serotype for Study CYD15 (FASE[1])

Treatment group	Cases[2]	Number of episodes	Person-years at risk	Density Incidence (95% CI)	%VE[3] (95% CI)
Dengvaxia N[4] = 13, 914 Any serotype	277	280	26,883	1.0 (0.9, 1.2)	64.7 (58.7, 69.8)
Placebo N = 6,940 Any serotype	385	388	13,204	2.9 (2.6, 3.2)	--

Treatment group	Cases[2]	Number of episodes	Person-years at risk	Density Incidence (95% CI)	%VE[3] (95% CI)
Dengvaxia Serotype 1	99	99	27,016	0.4 (0.3, 0.4)	54.8 (40.2, 65.9)
Placebo Serotype 1	109	109	13,434	0.8 (0.7, 1.0)	--
Dengvaxia Serotype 2	84	84	27,035	0.3 (0.2, 0.4)	50.2 (31.8, 63.6)
Placebo Serotype 2	84	84	13,461	0.6 (0.5, 0.8)	--
Dengvaxia Serotype 3	55	55	27,060	0.2 (0.2, 0.3)	74.2 (63.9, 81.7)
Placebo Serotype 3	106	106	13,459	0.8 (0.6, 1.0)	--
Dengvaxia Serotype 4	32	32	27,063	0.1 (0.1, 0.2)	80.9 (70.9, 87.7)
Placebo Serotype 4	83	83	13,442	0.6 (0.5, 0.8)	--
Dengvaxia Not serotyped	15	16	27,079	<0.1 (0.0, 0.1)	46.5 (-19.6, 75.9)
Placebo Not serotyped	14	14	13,514	0.1 (0.1, 0.2)	--

Source: Adapted from STN 125682/0 Clinical Study Report for CYD15 table 5.4 and 5.5
[1]FASE = Full analysis set for efficacy
[2]Cases: number of subjects with at least one symptomatic virologically-confirmed dengue episode throughout the Active Phase.
[3]VE = Vaccine efficacy, descriptive secondary endpoint
[4]N = Number in treatment group, FASE

During the active phase, one case of DHF (grade 2) out of 13,914 subjects was observed in the Dengvaxia group and 10 cases of DHF (two grade 1 and eight grade 2) out of 6,940 subjects occurred in the placebo group (table 6). The case observed in the Dengvaxia group occurred later than 28 days after the 3rd vaccine dose.

Table 6. Vaccine Efficacy Against Virologically-Confirmed Dengue Cases Meeting DHF WHO Criteria During the Active Phase Due to Any Serotype for Study CYD15 (FASE[1]).

Treatment group	Cases[2]	Number of episodes	Person-years at risk	Density Incidence (95% CI)	%VE[3] (95% CI)
Dengvaxia N[4] = 13,288 Any serotype	1	1	27,094	<0.1 (0.0, 0.0)	95.0 (64.9, 99.9)
Placebo N = 6,634 Any serotype	10	10	13,519	<0.1 (0.0, 0.1)	--

Source: Adapted from STN 125682/0 Clinical Study Report for CYD15 table 5.10
[1]FASE = Full analysis set for efficacy
[2]Cases: number of subjects with at least one symptomatic virologically-confirmed dengue episode throughout the Active Phase. One case of grade 2 DHF occurred in the Dengvaxia group; 2 cases of grade 1 DHF and 8 cases of grade 2 DHF occurred in the placebo group.
[3]VE = Vaccine efficacy, descriptive secondary endpoint
[4]N = Number in treatment group, FASE

The observed VE for Dengvaxia is influenced by baseline serostatus, with an estimated VE of 83.7% (95%CI: 62.2, 93.7) in dengue seropositive versus an estimated VE of 43.2 (95%CI: -61.6, 80.0) in dengue seronegative subjects (table 7). Limitations to the analysis include its post-hoc nature and small sample size since only about 10% (1,944/20,869) of subjects had baseline serostatus data collected.

Table 7. Vaccine Efficacy Against Virologically-Confirmed Dengue Cases During the Active Phase by Baseline Flavivirus Status for Study CYD15 (FASI[1])

Treatment group	Cases[2]	Number of episodes	Person-years at risk	Density Incidence (95% CI)	%VE[3] (95% CI)
Dengvaxia Dengue immune N[4] = 1,073	8	8	2,116	0.4 (0.2, 0.7)	83.7 (62.2, 93.7)
Placebo Dengue immune N = 512	23	23	994	2.3 (1.5, 3.5)	--
Dengvaxia Dengue non-immune N = 258	9	9	500	1.8 (0.8, 3.4)	43.2 (-61.6, 80.0)
Placebo Dengue non-immune N = 149	9	9	284	3.2 (1.5, 5.9)	--

Source: Adapted from STN 125682/0 Integrated Summary of Efficacy for CYD15 Table 3.4.5.38
[1]FASI = Full analysis set for immunogenicity
[2]Cases: number of subjects with at least one symptomatic virologically-confirmed dengue episode throughout the Active Phase.
[3]VE = Vaccine efficacy, descriptive secondary endpoint
[4]N = Number in immunogenicity subset

Study CYD15 Safety Results

Local Reactogenicity within 7 Days of Any Vaccination is described in table 8.

Table 8. Solicited Injection Site Reactions Within 7 Days After Each Injection for Study CYD15 (Reactogenicity Analysis Set)

Local Adverse Events (Any and Grade 3):	Dengvaxia N[1] = 1,278 - 1,326 n[2] (%)	Placebo N = 630 - 657 n (%)
Any pain:	--	--
Post-injection 1	430 (32.4)	173 (26.3)
Post-injection 2	332 (25.6)	105 (16.4)
Post-injection 3	288 (22.5)	104 (16.5)
Grade 3 pain	--	--
Post-injection 1	11 (0.8)	6 (0.9)
Post-injection 2	7 (0.5)	0 (0.0)
Post-injection 3	11 (0.9)	2 (0.3)
Any erythema:	--	--
Post-injection 1	55 (4.1)	31 (4.7)
Post-injection 2	25 (1.9)	11 (1.7)
Post-injection 3	19 (1.5)	10 (1.6)

Local Adverse Events (Any and Grade 3):	Dengvaxia N[1] = 1,278 - 1,326 n[2] (%)	Placebo N = 630 - 657 n (%)
Grade 3 erythema	--	--
Post-injection 1	0 (0.0)	1 (0.2)
Post-injection 2	1 (<0.1)	0 (0.0)
Post-injection 3	0 (0.0)	0 (0.0)
Any swelling:	--	--
Post-injection 1	47 (3.5)	18 (2.7)
Post-injection 2	25 (1.9)	6 (0.9)
Post-injection 3	20 (1.6)	8 (1.3)
Grade 3 swelling:	--	--
Post-injection 1	0 (0.0)	1 (0.2)
Post-injection 2	0 (0.0)	0 (0.0)
Post-injection 3	0 (0.0)	0 (0.0)

Source: Adapted from STN 125682/0 Clinical Study Report for CYD15 table 7.3
[1]N = Range of total number of subjects for which data were available,, reactogenicity analysis set
[2]n = Number of subjects experiencing the endpoint

Systemic Reactogenicity within 14 Days of Any Vaccination:
Headache was the solicited systemic reaction most frequently reported within 14 days after each injection (39.9% and 41.6% of subjects in the Dengvaxia and placebo groups, respectively) (table 9). The percentage of patients reporting headache was lower after subsequent injections in both groups.

Both treatment groups showed similar rates of the malaise, myalgia or asthenia episode after the first injection (around 25% - 30%), the frequencies of which decreased after subsequent injections and remained balanced. Most events were reported as mild to moderate (grade 1 or grade 2).

Table 9. Solicited Systemic Reactions Within 14 Days After Each Injection for Study CYD15 (Reactogenicity Analysis Set)

Systemic Adverse Events (Any and Grade 3)	Dengvaxia N[1] = 1,215 - 1,324 n[2] (%)	Placebo N[1] = 631 - 657 n (%)
Any fever:	**--**	**--**
Post-injection 1	86 (6.8)	42 (6.6)
Post-injection 2	72 (5.9)	42 (7.1)
Post-injection 3	89 (7.3)	52 (8.7)
Grade 3 fever:	--	--
Post-injection 1	21 (1.7)	7 (1.1)
Post-injection 2	10 (0.8)	7 (1.2)
Post-injection 3	13 (1.1)	5 (0.8)
Any headache:	--	--
Post-injection 1	528 (39.9)	273 (41.6)
Post-injection 2	386 (29.8)	182 (28.5)
Post-injection 3	378 (29.6)	158 (25.0)
Grade 3 headache:	--	--
Post-injection 1	67 (5.1)	27 (4.1)
Post-injection 2	27 (2.1)	15 (2.3)
Post-injection 3	33 (2.6)	12 (1.9)

Systemic Adverse Events (Any and Grade 3)	Dengvaxia N[1] = 1,215 - 1,324 n[2] (%)	Placebo N[1] = 631 - 657 n (%)
Any malaise:	--	--
Post-injection 1	324 (24.5)	170 (25.9)
Post-injection 2	270 (20.8)	106 (16.6)
Post-injection 3	246 (19.3)	96 (15.2)
Grade 3 malaise:	--	--
Post-injection 1	32 (2.4)	15 (2.3)
Post-injection 2	17 (1.3)	8 (1.3)
Post-injection 3	18 (1.4)	7 (1.1)
Any myalgia:	--	--
Post-injection 1	386 (29.2)	180 (27.4)
Post-injection 2	273 (21.0)	101 (15.8)
Post-injection 3	255 (20.0)	116 (18.4)
Grade 3 myalgia:	--	--
Post-injection 1	29 (2.2)	10 (1.5)
Post-injection 2	21 (1.6)	5 (0.8)
Post-injection 3	19 (1.5)	5 (0.8)
Any asthenia:	--	--
Post-injection 1	326 (24.6)	148 (22.5)
Post-injection 2	231 (17.8)	105 (16.4)
Post-injection 3	208 (16.3)	110 (17.4)
Grade 3 asthenia:	--	--
Post-injection 1	36 (2.7)	17 (2.6)
Post-injection 2	24 (1.8)	7 (1.1)
Post-injection 3	17 (1.3)	8 (1.3)

Source: Adapted from STN 125682/0 Clinical Study Report for CYD15 table 7.4
[1]N = Range of total number of subjects for which data were available, reactogenicity analysis set
[2]n = Number range of subjects experiencing the endpoint

Unsolicited AEs within 28 Days of Any Vaccination:
Unsolicited non-serious AEs were reported in 44.6% of subjects in the Dengvaxia Group and 44.0% in the placebo group within 28 days after any injection. The majority of unsolicited non-serious AEs occurred in the system organ class (SOC) “Infections and infestations” (25.8% and 26.4% in Dengvaxia and placebo groups, respectively) and reflected diagnoses commonly reported in childhood such as nasopharyngitis, influenza, rhinitis, tonsillitis, and viral infection. The next most commonly reported were from “Gastrointestinal disorders” (12.2% and 12.0% in the Dengvaxia and placebo groups, respectively) and reflected common childhood disorders such as abdominal pain, diarrhea, vomiting, odynophagia, and toothache. Frequencies of AEs from all other SOCs were < 10% and were balanced across groups.

SAEs and Deaths Occurring During the Active Phase:
See discussion of SAEs and deaths in Section 6 Integrated Summary of Safety.

4.2 Study CYD14

4.2.1 Study CYD14 Study Design

For CYD14, study design elements including primary efficacy objective, primary efficacy endpoint and success criterion; safety evaluations, duration of follow-up for the active

phase, definitions of the statistical analysis sets discussed in this briefing document, were identical to that of CYD15 with the following exceptions:

- CYD14 enrolled subjects ages 2 -14 years whereas CYD15 enrolled subjects ages 9 - 16 years.
- CYD14 enrolled subjects from Southeast Asia whereas CYD15 enrolled subjects from Central America, South America, and Puerto Rico.

Therefore, study design will not be discussed further except as pertinent to the data presented (please refer to Section 4.1.1 CYD15 Study Design instead).

4.2.2 Study CYD14 Results

Study CYD14 Trial Population:

Table 10 shows subject disposition and analysis groups that were used to evaluate the primary efficacy endpoint (PPSE) and safety endpoints (SAS and reactogenicity subset). Most subjects who withdrew (0.8%) did so voluntarily and not related to an AE (0.6%), were noncompliant with procedures or lost to follow-up (0.1% each). Five subjects (4 [0.1%] and 1 [0.1%], in Dengvaxia and placebo groups, respectively) did not complete the study due to an SAE. Based on nature and timing of vaccination only one was considered related to Dengvaxia (acute disseminated encephalomyelitis occurring on day 7 after the first injection). The subject recovered fully after 15 days.

Subjects were excluded from the per protocol efficacy and immunogenicity analysis sets (PPSE, and PPSI, respectively) largely because they either did not receive all three vaccinations or did not receive them within the prespecified time-frame.

Table 10. Analysis Groups for Subjects Enrolled to Study CYD14

Treatment Group	Dengvaxia n[1] (%)	Placebo n (%)	Total n (%)
Enrolled and randomized	6,851 (100)	3,424 (100)	10,275 (100)
Completed active phase	6,797 (99.2)	3,397 (99.2)	10,194 (99.2)
PPSE[2]	6,709 (97.9)	3,350 (97.8)	10,059 (97.9)
SAS[3]	6,848 (100)	3,424 (100)	10,272 (100)
Reactogenicity analysis set	1,334 (100)	663 (100)	1997 (100)
Full analysis set for immunogenicity	1,323 (99.0)	660 (99.4)	1,983 (99.1)

Source: Adapted from STN 125682/0 Clinical Study Report for CYD14 tables 4.1, 4.2, 10.15, 10.16, 10.17, and 10.18
[1]n = number per specified category in table
[2]PPSE = Per-Protocol Analysis Set for Efficacy
[3]SAS = Safety analysis set

Table 11 shows that subject age and sex were balanced across treatment groups. 100% of subjects reported Asian ethnicity.

Table 11. Demographics for Subjects Enrolled to Study CYD14 (SAS[1])

Treatment Group	Dengvaxia N[2] = 6,848	Placebo N = 3,424	Total N = 10,272
Male, n[3] (%)	3,324 (48.5)	1,657 (48.4)	4,981 (48.5)
Female, n (%)	3,524 (51.5)	1,767 (51.6)	5,291 (51.5)
Mean age in years (standard deviation)	8.8 (3.45)	8.8 (3.42)	8.8 (3.44)

Source: Adapted from STN 125682/0 Clinical Study Report for CYD14 table 10.22
[1]SAS = Safety analysis set
[2]N = Safety analysis set for by treatment group and total
[3]n = number per specified category in table

Study CYD14 Efficacy Results:
The primary efficacy endpoint was symptomatic VCD due to any of the 4 serotypes occurring >28 days after the 3rd vaccination for 12 months in subjects ages 2 -14 years. As shown in table 12, the prespecified success criterion for VE (LB of the 95%CI >25%) was met (56.5% [95%CI: 43.8, 66.4]) and was comparable to the primary efficacy results of CYD15 (table 4). Because the youngest age included in the proposed indication is 9 years, data for the 9-14 years were analyzed post hoc and results were comparable to VE observed for the full 2-14 years age group (table 12).

Table 12. Vaccine efficacy against symptomatic virologically-confirmed dengue post-dose 3 due to any of the 4 serotypes in subjects ages 2–14 years (PPSE[1]) and 9–14 years (FASE[2]) for study CYD14

Treatment group	Cases[3]	Number of episodes	Person-years at risk	Density Incidence (95% CI)	%VE[4] (95% CI)
Dengvaxia (PPSE) Ages 2 -14 years N[5] = 6,709	90	92	6,625	1.8 (1.5, 2.1)	**56.5 (43.8, 66.4)**
Placebo (PPSE) Ages 2 -14 years N = 3,350	136	139	3,224	4.1 (3.5, 4.9)	--
Dengvaxia (FASE) Ages 9 -14 years N = 3,316	13	13	3,187	1.4 (1.1, 1.7)	**67.8 (57.7, 75.6)**
Placebo (FASE) Ages 9 -14 years N = 1,656	21	21	1,566	4.2 (3.6, 5.0)	--

Source: Adapted from STN 125682/0 Clinical Study Report for CYD14 table 5.1 and integrated efficacy analysis table 3.6.5.7
[1]PPSE = Per protocol analysis set for efficacy
[2]FASE = Full analysis set for efficacy, cases were counted after the first dose.
[3]Cases: number of subjects with at least one symptomatic virologically-confirmed dengue episode from 28 days post-injection 3 to the end of Active Phase.
[4]VE = Vaccine efficacy, success criterion was met if the LB of the of the 95%CI for VE was >25% for the 2 -14 years age group.
[5]N = Number in treatment group, PPSE

Study CYD14 Additional Descriptive Analyses:
Because the youngest age included in the applicant's proposed indication is 9 years, analyses for the 9-14 years age group are considered more relevant to the BLA and will be shown for subsequent descriptive efficacy analyses (tables 13, 14, and 15). Importantly, VE for those ages 9 - 14 years were consistent with the VE results for the entire study population (ages 2-14 years).

Descriptive evaluation of VE against any strain occurring any time after the first dose throughout the active phase (table 13) was consistent with the analysis of the primary endpoint for VE in subjects 2 -14 years (estimated VE 54.8% [95%CI 46.8, 61.7]) as were analyses for VE for the individual dengue serotypes (not shown). Of note, although the point estimate for dengue 2 VE was 36.8%, the 95% CI included 0 (-10.1, 63.3).

Table 13. Vaccine Efficacy Against Symptomatic Virologically-Confirmed Dengue During the Active Phase Due to Each Serotype for Study CYD14 in Subjects Ages 9-14 years (FASE[1])

Treatment group (age)	Cases[2]	Number of episodes	Person-years at risk	Density Incidence (95% CI)	%VE[3] (95% CI)
Dengvaxia N[4] = 3,316 Any serotype	90	92	6,625	1.4 (1.1, 1.7)	67.8 (57.7, 75.6)
Placebo N = 1,656 Any serotype	136	139	3,224	4.2 (3.6, 5.0)	--
Dengvaxia Serotype 1	36	36	6,683	0.5 (0.4, 0.7)	65.7 (46.6, 78.2)
Placebo Serotype 1	52	52	3,306	1.6 (1.2, 2.1)	--
Dengvaxia Serotype 2	33	33	6,687	0.5 (0.3, 0.7)	36.8 (-10.1, 63.3)
Placebo Serotype 2	26	26	3,330	0.8 (0.5, 1.1)	--
Dengvaxia Serotype 3	11	11	6,715	0.2 (0.1, 0.3)	69.5 (31.9, 87.0)
Placebo Serotype 3	18	18	3,347	0.5 (0.3, 0.8)	--
Dengvaxia Serotype 4	10	10	6,716	0.1 (0.1, 0.3)	87.9 (75.5, 94.6)
Placebo Serotype 4	41	41	3,327	1.2 (0.9, 1.7)	--

Source: Adapted from STN 125682/0 Integrated Summary of Efficacy for CYD14 tables 3.6.5.7, 3.6.5.8, 3.6.5.9, 3.6.5.10 and 3.6.5.11

[1]FASE = Full analysis set for efficacy

[2]Cases: number of subjects with at least one symptomatic virologically-confirmed dengue episode throughout the Active Phase.

[3]VE = Vaccine efficacy, descriptive secondary endpoint

[4]N = Number in treatment group, FASE

During the active phase, 8 cases of DHF (two grade 1 and six grade 2) out of 6,848 subjects were observed in the Dengvaxia group and 20 cases of DHF (five grade 1, thirteen grade 2, and two grade 3) out of 3424 subjects occurred in the placebo group (table 14). Three of the cases in the Dengvaxia group and 13 of the cases in the placebo group occurred later than 28 days after the 3rd vaccine dose (table 14).

Table 14. Vaccine Efficacy Against Virologically-Confirmed Dengue Cases Meeting DHF WHO Criteria During the Active Phase Due to Any Serotype in Subjects Ages 9-14 years for Study CYD14 (FASE[1]).

Treatment group	Cases[2]	Number of episodes	Person-years at risk	Density Incidence (95% CI)	%VE[3] (95% CI)
Dengvaxia N[4] = 6,848 Any serotype	8	8	13,857	<0.1 (0.0, 0.0)	80.0 (52.7, 92.4)

Treatment group	Cases[2]	Number of episodes	Person-years at risk	Density Incidence (95% CI)	%VE[3] (95% CI)
Placebo N = 3,424 Any serotype	20	20	6,917	0.3 (0.2, 0.4)	--

Source: Adapted from STN 125682/0 Clinical Study Report for CYD14 table 5.4
[1]FASE = Full analysis set for efficacy
[2]Cases: number of subjects with at least one symptomatic virologically-confirmed dengue episode throughout the Active Phase.
[3]VE = Vaccine efficacy, descriptive secondary endpoint
[4]N = Number in treatment group, FASE

As with study CYD15, the observed VE for Dengvaxia is influenced by baseline serostatus, with an estimated VE of 74.3% (95%CI: 53.2, 86.3) in dengue seropositive versus an estimated VE of 35.4% (95%CI: -27.0, 66.6) in dengue seronegative subjects (table 15). Limitations to the analysis include its post-hoc nature and small sample size for those 9-14 years of age participating in the immunogenicity subset.

Table 15. Vaccine Efficacy Against Virologically-Confirmed Dengue Cases During the Active Phase by Baseline Flavivirus Status in Subjects Ages 9–14 Years for Study CYD14 (FASI[1])

Treatment group	Cases[2]	Number of episodes	Person-years at risk	Density Incidence (95% CI)	%VE[3] (95% CI)
Dengvaxia Dengue immune N[4] = 487	7	7	981	0.7 (0.3, 1.5)	79.2 (53.2, 86.3)
Placebo Dengue immune N = 251	17	18	496	3.4 (2.0, 5.4)	--
Dengvaxia Dengue non-immune N = 129	7	8	256	2.7 (1.1, 5.6)	61.6 (-21.1, 88.1)
Placebo Dengue non-immune N = 59	8	8	112	7.1 (3.1, 13.6)	--

Source: Adapted from STN 125682/0 Integrated Summary of Efficacy for CYD14 Table 3.6.5.15
[1]FASI = Full analysis set for immunogenicity
[2]Cases: number of subjects with at least one symptomatic virologically-confirmed dengue episode throughout the Active Phase.
[3]VE = Vaccine efficacy, descriptive secondary endpoint
[4]N = Number in immunogenicity subset

Study CYD14 Safety Results

Solicited local and systemic reactions were mostly mild to moderate severity and rates were consistent with results shown for CYD15 (tables 8 and 9). Therefore, these results will not be discussed further. Similarly, unsolicited AEs did not reveal imbalances between treatment groups and were consistent with the nature and frequency of events observed in CYD15. SAEs and deaths will be discussed in Section 6 Integrated Summary of Safety.

4.3 Study CYD23

4.3.1 Study CYD23 Study Design

As with CYD14, CYD23 study design elements including primary efficacy objective, primary efficacy endpoint and success criterion; safety evaluations, duration of follow-up for the active phase, and definitions of the statistical analysis sets discussed in this briefing document, were identical to that of CYD15 with the following exceptions:

- Study CYD23 was phase IIb versus CYD15 and CYD14 which were phase III.
- CYD23 enrolled subjects ages 4 – 11 years whereas CYD15 enrolled subjects ages 9 - 16 years.
- CYD23 enrolled subjects from a single site in Thailand whereas CYD15 enrolled subjects from Central America, South America, and Puerto Rico.

Therefore, study design will not be discussed further except as pertinent to the data presented (please refer to Section 4.1.1 CYD15 Study Design).

4.3.2 Study CYD23 Results

Study CYD23 Trial Population:

Table 16 shows subject disposition and analysis groups that were used to evaluate the primary efficacy endpoint (PPSE) and the safety endpoints (SAS). Of note, most patients who withdrew (4.3%) did so voluntarily and not related to an AE (2.5%) or were noncompliant with procedures (1.1%). No subjects were withdrawn from the Dengvaxia group for an SAE. Subjects were excluded from the efficacy analysis largely because they either did not receive all three vaccinations or did not receive them within the prespecified time-frame.

Table 16. Analysis Groups for Subjects Enrolled to Study CYD23

Treatment Group	Dengvaxia n[1] (%)	Placebo n (%)	Total n (%)
Enrolled and randomized	2,669 (100)	1,333 (100)	4,002 (100)
Completed active phase	2,552 (95.6)	1,276 (95.7)	3,828 (95.7)
PPSE[2]	2,452 (92.0)	1,221 (91.7)	3,673 (91.9)
SAS[3]	2,666 (99.9)	1,331 (99.8)	3,997 (99.9)

Source: Adapted from STN 125682/0 Clinical Study Report for CYD23 tables 4.1, 4.2, 4.3, 9.25.
[1]n = number per specified category in table
[2]PPSE = Per-Protocol Analysis Set for Efficacy (see definition in Section 4.1, *Selected Analysis Populations*)
[3]SAS = Safety analysis set

Table 17 shows that the demographic data (age and sex) were balanced across treatment groups. All subjects enrolled from this single center study were Thai.

Table 17. Demographics for Subjects Enrolled to Study CYD23 (SAS[1])

Treatment Group	Dengvaxia N[1] = 2,666	Placebo N = 1,331	Total N = 3,997
Male, n[2] (%)	1,290 (48.4)	635 (47.7)	1,925 (48.2)
Female, n (%)	1,376 (51.6)	696 (52.3)	2,072 (51.8)
Mean age in years (standard deviation)	8.16 (2.03)	8.20 (2.05)	8.17 (2.03)

Source: Adapted from STN 125682/0 Clinical Study Report for CYD23 table 4.4
[1]SAS = Safety analysis set
[2]N = Safety analysis set for by treatment group and total
[3]n = number per specified category

Study CYD23 Primary Efficacy Results

The primary efficacy endpoint was symptomatic VCD due to any of the 4 serotypes occurring >28 days after the 3rd vaccination for 12 months. As shown in table 18, although the point estimate for VE was 30.2% (95%CI: -13.4, 56.6) the prespecified success criterion for VE (LB of the 95%CI >0%) was not met. In the post hoc subgroup analysis of subjects ages 9 – 11, VE was 70.1% (95%CI: 9.3, 91.1).

Table 18. Vaccine Efficacy Against Symptomatic Virologically-Confirmed Dengue Post-Dose 3 Due to Any of the 4 Serotypes for Study CYD23 (PPSE[1])

Treatment group	Cases[2]	Number of episodes	Person-years at risk	Density Incidence (95% CI)	%VE[3] (95% CI)
Dengvaxia Ages 4-11 years N[4] = 2,452	45	45	2,522	1.8 (1.3, 2.4)	**30.2 (-13.4, 56.6)**
Placebo Ages 4–11 years N = 1,221	32	33	1,251	2.6 (1.8, 3.6)	--
Dengvaxia Ages 9-11 years N = 1,011	6	6	1,033	0.6 (0.2, 1.3)	**70.1 (9.3, 91.1)**
Placebo Ages 9-11 years N = 502	10	10	514	1.9 (0.9, 3.5)	--

Source: Adapted from STN 125682/0 Clinical Study Report for CYD23 table 5.1, and Integrated Summary of Efficacy table 3.6.5.2

[1]PPSE = Per-protocol analysis set for efficacy

[2]Cases: number of subjects with at least one symptomatic virologically-confirmed dengue episode from 28 days post-injection 3 to the end of Active Phase.

[3]VE = Vaccine efficacy, success criterion was met if the LB of the of the 95%CI for VE was >0% for the 4 – 11 years age group

[4]N = Number in treatment group, PPSE

Study CYD23 Additional Descriptive Analyses:

Because the youngest age included in the applicant's proposed indication is 9 years, analyses for the 9 -11 years age group are considered more relevant to the BLA and will be shown for subsequent descriptive efficacy analyses (table 19).

Table 19. Vaccine Efficacy Against Symptomatic Virologically-Confirmed Dengue During the Active Phase Due to Each Serotype for Study CYD23 in Subjects Ages 9-11 Years (FASE[1])

Treatment group	Cases[2]	Number of episodes	Person-years at risk	Density Incidence (95% CI)	%VE[3] (95% CI)
Dengvaxia N[4] = 1,032 Any serotype	18	18	2,066	0.9 (0.5, 1.4)	43.3 (-18.9, 72.7)
Placebo N = 522 Any serotype	16	16	1,042	1.5 (0.9, 2.5)	--
Dengvaxia Serotype 1	3	3	2,083	0.1 (0.0, 0.4)	78.4 (5.4, 96.4)

Treatment group	Cases[2]	Number of episodes	Person-years at risk	Density Incidence (95% CI)	%VE[3] (95% CI)
Placebo Serotype 1	7	7	1,050	0.7 (0.3, 1.4)	--
Dengvaxia Serotype 2	13	13	2,072	0.6 (0.3, 1.1)	5.9 (-178.6, 65.1)
Placebo Serotype 2	7	7	1,050	0.7 (0.3, 1.4)	--
Dengvaxia Serotype 3	2	2	2,083	<0.1 (0.0, 0.3)	- 1.2 (-5,870.2, 94.7)
Placebo Serotype 3	1	1	1,054	<0.1 (0.0, 0.5)	--
Dengvaxia Serotype 4	0	0	2,087	0.0 (0.0, 0.2)	100.0 (-1,873.3; 100.0)
Placebo Serotype 4	1	1	1,056	<0.1 (0.0, 0.5)	--

Source: Adapted from STN 125682/0 Integrated Summary of Efficacy for CYD23 table 3.6.5.7, 3.6.5.8, 3.6.5.9, 3.6.5.10, and 3.6.5.11
[1]FASE = Full analysis set for immunogenicity
[2]Cases: number of subjects with at least one symptomatic virologically-confirmed dengue episode throughout the Active Phase.
[3]VE = Vaccine efficacy, descriptive secondary endpoint
[4]N = Number in treatment group, FASE

As with studies CYD15 and CYD14, analyses of VE for cases of severe dengue disease and DHF was evaluated in study CYD23. However, there were insufficient cases to draw meaningful conclusions from these analyses for either the entire study population (1 case of severe dengue disease in the Dengvaxia group and 2 cases in the placebo group) or the 9 – 11 years age group.

As with studies CYD15 and CYD14, VE based on prevaccination dengue serostatus was assessed, but there were too few cases for which this information was known to draw meaningful conclusions.

5.0 Immunogenicity Data Supporting Use in Adults Ages 18-45 Years

Three studies conducted in dengue-endemic regions [CYD22 (Vietnam); CYD28 (Singapore), and CYD47 (India)] contribute descriptive immunogenicity data to support use of Dengvaxia in adults ages 18-45 years.

5.1 Description of the Study Designs, Objectives, and Endpoints

Each of the supportive studies in adults was randomized and observer-blinded with the main immunogenicity objective being descriptive dengue humoral immune responses before and after each injection. While studies CYD22 and CYD28 enrolled children and adults, only immune response data from adults enrolled in these studies are described below.

Immune responses were assessed by measurement of dengue serotype-specific neutralizing antibodies using a plaque reduction neutralization assay with a 50% neutralization endpoint ($PRNT_{50}$). This is the highest serial 2-fold dilution of serum at which ≥ 50% of dengue challenge virus (in plaque counts) is neutralized. Dengue-immune

subjects were those with titers ≥ 10 (1/dilution) against at least one dengue serotype at baseline.

5.2 Immunogenicity Results

A specific threshold $PRNT_{50}$ titer above which vaccine effectiveness could be predicted reliably was not identified for any dengue serotype. Therefore, serotype-specific GMTs, rather than percentages of subjects achieving a specific neutralizing antibody titer, were used to compare vaccine responses among dengue immune adolescents in the efficacy studies with vaccine responses of dengue-immune adults to support use of Dengvaxia in dengue-immune adults.

Immunogenicity subsets from the efficacy studies were comprised of approximately 20% of subjects in CYD14 and 10% of subjects in CYD15; these subjects had blood draws for assessment of $PRNT_{50}$ at baseline and at 1 month after the 3rd dose. Table 20 summarizes GMTs from the three supportive studies in adults from endemic regions who were dengue-immune at baseline, and GMTs from the subgroups of vaccinated subjects 9-17 years of age who were dengue-immune at baseline in each of two clinical efficacy studies.

No statistical criteria were pre-specified for assessing comparability of GMTs from adults to GMTs observed in the clinical efficacy studies. Descriptively, in studies CYD22 and CYD47 where dengue endemicity was established, post-dose 3 GMTs among vaccinated dengue-immune adults ages 18-45 years of age were similar to post-dose 3 GMTs of dengue-immune vaccinated subjects ages 9-16 years in the immunogenicity subsets from efficacy studies CYD14 and CYD15 that were also conducted in dengue-endemic regions. Singapore, the study site for CYD28, was characterized as a dengue endemic region, but was composed of subjects who had lower baseline GMTs compared with adult subjects from study sites in Vietnam and India.

Table 20: Geometric Mean Serum Neutralizing Antibody Titers (GMT) by Serotype Among Vaccinated Dengue-Immune Children and Adolescents 9-16 Years of Age from Efficacy Studies (CYD14, CYD15) and Among Vaccinated Dengue-Immune Adults 18-45 Years of Age from Endemic Regions in Supporting Studies (CYD22, CYD28, CYD47)

Study/Region (Age Group)	N[1]	Serotype 1 Pre-dose 1 GMT (95% CI)	Serotype 1 Post-dose 3 GMT (95% CI)	Serotype 2 Pre-dose 1 GMT (95% CI)	Serotype 2 Post-dose 3 GMT (95% CI)	Serotype 3 Pre-dose 1 GMT (95% CI)	Serotype 3 Post-dose 3 GMT (95% CI)	Serotype 4 Pre-dose 1 GMT (95% CI)	Serotype 4 Post-dose 3 GMT (95% CI)
CYD14 Asia/Pacific (9-14 years)	477-483	**167** (138; 202)	**437** (373; 511)	**319** (274; 373)	**793** (704; 892)	**160** (135; 190)	**443** (387; 507)	**83.8** (72.0; 97.6)	**272** (245; 302)
CYD15 L Am. (9-16 years)	1,040-1,048	**278** (247; 313)	**703** (634; 781)	**306** (277; 338)	**860** (796; 930)	**261** (235; 289)	**762** (699; 830)	**73.3** (66.6; 80.7)	**306** (286; 328)
CYD22 Vietnam (18-45 years)	17-19	**408** (205; 810)	**785** (379; 1626)	**437** (240; 797)	**937** (586, 1,499)	**192** (117; 313)	**482** (357; 651)	**86.5** (41.2; 182)	**387** (253; 591)
CYD28 Singapore (18-45 years)	55-66	**59.8** (36.8; 97.4)	**235** (135; 409)	**67.1** (40.9; 110)	**236** (144; 387)	**48.4** (32.9; 71.0)	**239** (166; 342)	**22.1** (14.7; 33.4)	**211** (155; 287)
CYD47 India (18-45 years)	98-109	**324** (236; 445)	**688** (524; 901)	**363** (269; 490)	**644** (509; 814)	**394** (299; 519)	**961** (763; 1,211)	**80.7** (61.3; 106)	**413** (331; 516)

Source: Adapted from BLA 125682, Integrated Immunogenicity Analysis Report, Table 3.9.4.6
[1]N refers to number of sera assayed by $PRNT_{50}$ which varied by serotype.
Dengue-immune subjects are those with titers ≥ 10 (1/dilution) against at least one dengue serotype at baseline.

These immunogenicity data are intended to support effectiveness of Dengvaxia in dengue-immune persons 17 through 45 years of age, living in endemic areas.

6.0 Integrated Summary of Safety

6.1 Overall Safety Profile

In order to assess the overall safety profile of the vaccine in the age group intended for use, a pool of data from subjects 9 to 45 years of age was assembled and analyzed. This dataset included 20,426 subjects who received the final formulation according to the intended regimen (0, 6, and 12 months). Table 21, below, displays rates of notable safety outcomes in Dengvaxia recipients compared with placebo recipients up to 6 months after any dose.

Table 21. Safety Overview after Any Dengvaxia or Placebo Dose - Subjects 9-45 Years of Age

Subjects experiencing at least one:	Dengvaxia n[1] (N[2] = 20,426)	Dengvaxia % (95% CI)	Placebo n (N = 9,768)	Placebo % (95% CI)
SAE <=28 days post dose	134	0.7 (0.55; 0.78)	74	0.8 (0.60; 0.95)
SAE >28 days to 6 months post dose	575	2.8 (2.59; 3.05)	313	3.2 (2.86; 3.57)
Neurological disorder SAE <=30 days post dose	15	<0.1 (0.04; 0.12)	9	<0.1 (0.04; 0.17)
Neurological disorder SAE >30 days to 6 months post dose	28	0.1 (0.09; 0.20)	13	0.1 (0.07; 0.23)
Serious allergic reaction	5	<0.1 (0.01; 0.06)	1	<0.1 (0.00; 0.06)
Discontinuation due to AE	82	0.4 (0.32; 0.50)	39	0.4 (0.28; 0.55)
Death within 6 months post dose	5	<0.1 (0.01; 0.06)	4	<0.1 (0.01; 0.10)

Source: Adapted from STN 125682/0 Summary of Clinical Safety; Table 23.
[1]n: number of subjects experiencing the endpoint
[2]N: number of subjects with available data for the relevant endpoint
Contributing studies: CYD12 CYD13 CYD14 CYD15 CYD17 CYD22 CYD23 CYD24 CYD28 CYD30 CYD32 CYD47 CYD51

The pooled analysis in subjects 9 through 45 years of age included review of the pattern and types of SAEs stratified by multiple variables, such as age and baseline serostatus, and this review did not reveal a safety signal with respect to SAEs . These analyses, which evaluated outcomes up to 6 months after each dose, did not include cases of dengue disease. The risk of hospitalized VCD is discussed below (Section 6.2).

The reactogenicity of the vaccine was assessed via solicitation for specific local (e.g., erythema, induration) and systemic (e.g., fever, myalgia) adverse reactions in a subset of subjects in select studies. There were no unexpected findings in the analyses of reactogenicity. The relevant data are displayed in the review of the individual studies in Section 4.

6.2 Risk of Hospitalized Virologically-Confirmed Dengue (VCD)

Early in clinical development, the sponsor integrated into their program a systematic approach to long term surveillance to assess the risk of severe dengue disease. As a result, the pivotal clinical endpoint efficacy studies, CYD23, CYD14, and CYD15, were conducted according to a similar design: ~2 year "Active Phase" (the one year needed to complete the regimen, along with a one year period for accruing primary efficacy endpoint cases) followed by a three year "Hospital Phase", during which the sponsor identified and assessed hospitalized VCD.* See Section 4.1.1 for details of the study design of CYD14, which is representative of CYD23 and CYD15 as well.

* In order to collect more detailed information on all dengue cases, including those that did not result in hospitalization, the sponsor revised their approach during the "Hospital Phase" to re-establish active surveillance comparable to what was done during the "Active Phase". Therefore, the "Hospital Phase" of CYD14 and CYD15 includes the establishment of a Surveillance Enhancement Period (SEP), during which "Active Phase" surveillance was added to the ongoing surveillance for hospitalized VCD. Because this is likely to have had no meaningful impact on the rates of hospitalized VCD identified or the analyses relevant to the safety signal for hospitalized VCD in seronegative subjects, the SEP will not be further addressed in this briefing document.

As shown in Table 22, below, a pooled analysis of all subjects 9 to 16 years of age from studies CYD14, CYD15, and CYD23 indicated that the risk of hospitalized VCD was lower for Dengvaxia recipients compared with placebo recipients, both during the entire 60 month follow-up period post-dose 1 and during each of the individual years of Hospital Phase surveillance.

Table 22. Pooled CYD14, CYD15 and CYD57 - Incidence of Hospitalized VCD Cases Due to Any Serotype During Follow-Up and Over the Entire Study Period – Subjects 9-16 Years of Age

Time Period	Dengvaxia Cases[1]/M[2]	Dengvaxia Annual Incidence Rate[3] (95% CI)	Placebo Cases/M	Placebo Annual Incidence Rate (95% CI)	Relative Risk (95% CI)
Year 1 Hospital Phase	27/17,349	0.2 (0.1; 0.2)	27/8,680	0.3 (0.2; 0.5)	0.500 (0.28; 0.89)
Year 2 Hospital Phase	28/17,081	0.2 (0.1; 0.2)	25/8,567	0.3 (0.2; 0.4)	0.562 (0.32; 1.00)
Year 3 Hospital Phase	21/15,934	0.1 (0.1; 0.2)	19/7,920	0.2 (0.1; 0.4)	0.549 (0.28; 1.08)
Year 1+2+3	76/16,788	0.2 (0.1; 0.2)	71/8,389	0.3 (0.2; 0.4)	0.535 (0.38; 0.75)
Entire Study Period*	109/17,292	0.1 (0.1; 0.2)	151/8,638	0.3 (0.3; 0.4)	0.361 (0.28; 0.46)

Source: Adapted from STN 125682/0 Clinical Overview, Table 9.
[1]Cases: number of subjects with at least one hospitalized virologically-confirmed dengue episode.
[2]M: number of subjects present at the beginning of each year or mean of number of subjects followed during the years included.
[3]The annual Incidence rate = Cases among M * 100 converted in annual rate.
*Entire study period includes data from Active Phase period

During the Hospital Phase follow-up, in analyses stratified by age, a safety signal for increased risk of hospitalized VCD in younger subjects (particularly 2 to 5 years of age) became apparent. Dengue exposure tracks with age, so these findings raised the possibility that absence of pre-existing dengue immunity predisposed vaccinated subjects to severe disease. Because pre-vaccination blood was drawn on only a subset (~2,000 subjects; the "immunogenicity subset") of the overall efficacy study population, pre-vaccination serostatus was not available for the majority of subjects who became hospitalized VCD cases during the Hospital Phase. Therefore, no definitive conclusions could be reached about the signal of risk in the baseline seronegative population.

In order to further investigate and characterize this safety signal, the sponsor used an ELISA assay against the dengue virus protein NS1. In contrast to the dengue neutralization assay ($PRNT_{50}$ – see Section 5.1 for details), the NS1 assay can distinguish the immune response to vaccination from the immune response to natural dengue exposure. It was possible to optimize this feature of the assay because of the difference between NS1 in the yellow fever virus backbone of the vaccine compared with NS1 expressed by wild type dengue virus. By running the NS1 assay on stored sera that had been collected from subjects post-dose 3, the sponsor was able to determine with reasonable accuracy whether the subjects who became hospitalized VCD cases were dengue immune or non-immune at the beginning of the study. The resulting data were used to impute baseline serostatus for a series of exploratory analyses to assess the risk of hospitalized VCD.

The signal for risk identified in the immunogenicity subset analyses was replicated and more fully characterized by the similar results obtained in the NS1 imputation analyses. Select, relevant NS1-derived analyses are displayed below.

Table 23 displays the Hazard Ratio for hospitalized VCD stratified by baseline serostatus among all subjects 9 to 16 years of age from each clinical endpoint efficacy study and for all studies pooled.

Table 23. Risk of Hospitalized VCD During the Entire Study Period Among Subjects 9 to 16 Years of Age from CYD14, CYD15, CYD23/57, and All Studies Pooled – Stratified by Dengue Serostatus*

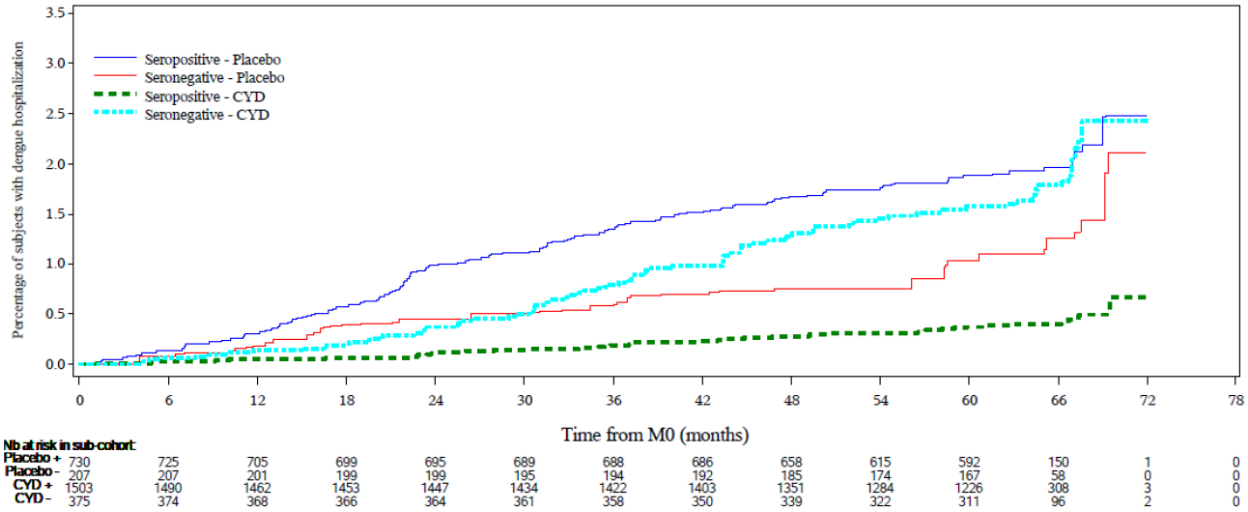
Baseline status	Study	Dengvaxia n[1](N[2])	Placebo n(N)	Hazard Ratio (95% CI)
Seropositive	CYD14	10.3 (61.4)	21.6 (32.6)	0.277 (0.165, 0.467)
--	CYD15	20.3 (1,146.9)	63.6 (546)	0.149 (0.082, 0.271)
--	CYD23/57	10.3 (61.4)	21.6 (32.6)	0.252 (0.089, 0.714)
--	All studies pooled	58.8 (1,502.9)	137.7 (729.8)	0.206 (0.138, 0.307)
Seronegative	CYD14	27.8 (77.4)	13.5 (32.8)	0.921 (0.412, 2.060)
--	CYD15	25.7 (276.1)	7.4 (161)	2.174 (0.497, 9.512)
--	CYD23/57	10.7 (21.6)	4.4 (13.4)	1.695 (0.216, 13.302)
--	All studies pooled	64.2 (375.1)	25.3 (207.2)	1.412 (0.743, 2.682)

Source: Adapted from STN 125682/0 Clinical Overview, Table 10.
[1]n: number of subjects fulfilling the item listed
[2]N: total number of subjects selected in sub-cohort
n and N are average numbers from 10 iterations of multiple imputations
*Serostatus measured by PRNT or imputed by NS1
Randomization ratio Dengvaxia/control groups 2:1

Although the Hazard Ratio for hospitalized VCD among seronegative subjects crosses 1 for each of the studies and for the pooled analysis, these data strongly suggest that in a dengue non-immune population, vaccination increases the risk of hospitalized VCD.

Figure 2, below, plots cases of hospitalized VCD on a Kaplan-Meier curve, stratified by baseline serostatus. This figure illustrates the kinetics of the risk of hospitalized VCD in the population of subjects 9 to 16 years of age pooled from all the efficacy studies (CYD14, CYD15, and CYD23).

Figure 2. Kaplan-Meier Curve of time to dengue hospitalization from M0 in subjects aged 9 to 16 years at enrollment - serostatus classified by PRNT50 at baseline or NS1 (multiple imputation approach)



Source: Adapted from STN 125682/0 Clinical Overview, Figure 15.
Numbers at risk are average numbers from 10 iterations of multiple imputations.
Data pooled from CYD14, CYD15, and CYD23/57.

Figure 2 suggests that the vaccine may be transiently protective against hospitalized VCD in a dengue non-immune population. However, that protective effect appears to shift to an increased risk at ~18 months after completion of the vaccination regimen (30 months post-dose 1). This suggests that in dengue non-immune individuals, receipt of vaccine could have an impact similar to that of an initial dengue infection, in that protective immunity rapidly wanes, leading to an antibody repertoire (and/or broader immune profile) that predisposes to severe disease in the event of a subsequent dengue infection. These data also suggest that, in contrast to the dengue non-immune population, the dengue immune population may benefit from durable protection against hospitalized VCD (although no firm conclusions can be drawn, given that the analyses were post-hoc and based in part on imputation/modeling).

The data and analyses summarized in this subsection were the basis for the sponsor's decision to exclude dengue non-immune individuals from the proposed indication. Thus, the sponsor is requesting approval for use only for individuals 9 through 45 years of age with laboratory-confirmed previous dengue infection and living in endemic areas.

6.3 Vaccine strain viremia and shedding

Viremia

Post-vaccination vaccine viremia was assessed by quantitative RT-PCR in a subset of subjects in multiple clinical studies. In general, the rates of vaccine virus viremia were low. Across the pooled studies, 3.8% of subjects had detectable viremia by RT-PCR following the first dose. Rates were lower after the second or third dose. Viremia, if present, was typically detected ~Day 7 post-vaccination. The duration was typically short, and no viremia was detected after Day 14 post-vaccination. The detection of viremia did not appear to be correlated with any concerning safety outcomes.

Shedding
Yellow Fever vaccine virus and wild type dengue virus have both been detected in urine and saliva post-exposure. To investigate the potential for vaccine virus shedding after receipt of Dengvaxia, urine and saliva samples were tested in a subset of subjects in CYD04 and CYD17. From the group of 106 subjects tested, RT-PCR was positive near the lower limits of quantitation (LLOQ) in the urine sample from 2 subjects. No replication-competent virus was detected in any sample. No safety concerns were noted in the relevant 2 subjects.

6.4 Use in Special Populations

Pediatric
The sponsor is seeking an indication for use of the vaccine in individuals 9 to 45 years of age. Therefore, data in individuals <9 years of age are not analyzed or described in any depth in this briefing document. The sponsor has indicated that they plan to conduct additional studies to better characterize the safety and effectiveness of the vaccine in individuals <9 years of age.

Elderly
In the clinical development program, some studies included individuals up to 60 years of age. However, the sponsor is not seeking an indication for use above the age of 45 years, as the available data on subjects 46 to 60 years of age were limited. Therefore, no further discussion regarding use in an elderly population is necessary at this time.

Pregnancy
In all the clinical studies conducted with Dengvaxia, pregnancy was an exclusion criteria and pregnancy testing was done prior to administration of each dose of vaccine. Despite these procedures, a number of females were vaccinated shortly before or early in pregnancy. The pregnancy was considered as “exposed to the study vaccine when the subject was pregnant” if the subject received the injection 7 days after her last menstrual period (LMP) or 7 days before the estimated date of conception or later. The pregnancy was considered as “exposed to the study vaccine but not yet pregnant” if the subject received the injection during the interval between 30 days before her LMP and 7 days after her LMP (which also corresponds to the period between 44 days and 7 days before conception). All other pregnancies were considered as “unexposed”.

A total of 404 pregnancies were reported in subjects who received the CYD dengue vaccine from completed studies or during the Active Phase of CYD14 and CYD15 studies: 341 were unexposed, 36 were exposed but not yet pregnant, 22 were exposed and pregnant, and exposure could not be determined for 5 pregnancies. Among the 22 female subjects who received Dengvaxia during their pregnancy, 3 had adverse pregnancy outcome (death in utero, stillbirth and blighted ovum). In each case, important risk factors were identified.

Although these data do not suggest a specific safety concern, they are not adequate to support the safety of use during pregnancy. The package insert proposed by the sponsor includes pregnancy as a contraindication.

Immunocompromised individuals
Throughout the clinical development program, eligibility criteria resulted in exclusion of individuals with immunocompromising conditions, including HIV and individuals on immunomodulatory medications. Therefore, no data are available on the safety or effectiveness of the vaccine in this population.

7.0 Pharmacovigilance Plan

Sanofi Pasteur submitted a Pharmacovigilance Plan to monitor safety concerns that could be associated with Dengvaxia. The applicant identified as important risks allergic reactions and severe and hospitalized dengue in individuals not previously infected by dengue virus. To mitigate the increased risk of severe and hospitalized dengue in individuals not previously infected with dengue virus, the requested indication for Dengvaxia includes use only in individuals 9 through 45 years of age, with laboratory-confirmed previous dengue infection, and residing in endemic areas. To further mitigate the identified risks and to surveil for new safety signals, the applicant proposes both routine and enhanced pharmacovigilance activities that will include: routine monitoring of spontaneous safety reports and periodic aggregate review of worldwide safety data; targeted questionnaires to document allergic adverse events of special interest and dengue infections amongst Dengvaxia recipients; completion of long-term follow-up from the Phase 3 trials, CYD14 and CYD15; a prospective cohort study with active safety surveillance up to 5 years post-vaccination of 30,000 Dengvaxia recipients in Brazil, Mexico, and the Philippines; and a pregnancy registry to monitor maternal and infant outcomes in pregnant women inadvertently exposed to Dengvaxia. Additional pharmacovigilance activities proposed for the U.S. include ongoing surveillance to assess the risks of dengue infection and severe and hospitalized dengue infection in endemic regions in the U.S. where Dengvaxia is administered. The details of these additional pharmacovigilance activities remain under discussion between FDA and the applicant.

8.0 Summary and Focus of Questions to the Committee

In studies CYD15 and CYD14, after three subcutaneously administered doses of Dengvaxia for subjects 9 through 16 years of age, VE against VCD was 60.8% [95% CI: (52.0%, 68.0%)] and 67.8% [95% CI: (57.7%, 75.6%)], respectively. For subjects 9 through 16 years who were seropositive for a prior dengue infection at baseline, the VE against VCD was 83.7% [95% CI: (62.2%, 93.7%)] for CYD15 and 79.2% [95% CI: (47.2%, 92.7%)] for CYD14. In study CYD23, VE against VCD was not demonstrated, presumably due to relatively lower VE against serotype 2 which was most prevalent in that study. In studies CYD22 and CYD47, the immunogenicity (measured 28 days post-dose 3) in subjects 18 through 45 who were seropositive for a prior dengue infection at baseline was similar to the immunogenicity in subjects 9 through 16 years in CYD14 and CYD15 who were seropositive for a prior dengue infection at baseline.

An increased risk of hospitalized VCD was observed in Dengvaxia recipients who were seronegative at baseline.

Regarding reactogenicity, the majority of subjects experienced local and/or general adverse reactions of short duration. Most reactions were mild or moderate (grade 1 or grade 2) and no substantial imbalances in severe reactions were evident between Dengvaxia and placebo groups. Overall, SAEs (excluding hospitalized VCD) and deaths were reported in similar proportions of subjects in Dengvaxia and placebo groups included in the submitted safety database.

The Committee will be asked whether the safety, efficacy, and immunogenicity data support licensure of Dengvaxia for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in individuals 9 through 45 years of age with laboratory-confirmed previous dengue infection and living in endemic areas.

9.0 References:

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