BLA Clinical Review Memorandum

Application Type	Original Application
STN	125682/0
CBER Received Date	08/31/2018
PDUFA Goal Date	05/01/2019
Division / Office	DVRPA/OVRR
Priority Review (Yes/No)	Yes
Reviewer Name(s)	Ralph LeBlanc, M.D., Ph.D. Medical Officer
Review Completion Date / Stamped Date	
Supervisory Concurrence	Lucia Lee, M.D., Team Leader Roshan Ramanathan, M.D., M.P.H., Branch Chief
Applicant	Sanofi Pasteur, Inc.
Established Name	Dengue Tetravalent Vaccine, Live
Trade Name	Dengvaxia
Pharmacologic Class	Vaccine
Formulation	When Dengvaxia is reconstituted with saline diluent (0.4% sodium chloride), each dose (0.5mL) contains 4.5 – 6.0 $\log_{10}$ $CCID_{50}$ of each chimeric yellow fever dengue (CYD) virus serotypes 1, 2, 3, and 4.
Dosage Form and Route of Administration	Suspension, subcutaneous
Dosing Regimen	3-dose series [Months 0, 6 and 12].
Indication(s) and Intended Population(s)	Active immunization for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in individuals 9 through 16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas.
Orphan Designated (Yes/No)	No

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GLOSSARY

Glossary

AA	Accelerated Approval
AE	adverse event
BLA	biologics license application
CBER	Center for Biologics Evaluation and Research
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
CYD	Chimeric Yellow Fever Dengue
DHF	Dengue Hemorrhagic Fever
eCTD	electronic Common Technical Document
ELISA	Enzyme-Linked Immunosorbent Assay
ES	Executive Summary
FDAAA	Food and Drug Administration Amendments Act of 2007
GRMP	good review management principles
ISE	integrated summary of efficacy
ITT	intent-to-treat
MedDRA	Medical Dictionary for Regulatory Activities
OBE	Office of Biostatistics and Epidemiology
OCOD	Office of Communication Outreach and Development (CBER)
OSE	Office of Surveillance and Epidemiology
PD	pharmacodynamics
PeRC	Pediatric Review Committee (CDER)
PI	package insert
PK	pharmacokinetics
PMC	post marketing commitment
PMR	post marketing requirement
PREA	Pediatric Research Equity Act
PRNT50	Plaque Reduction Neutralization Titer at 50%
PSP	Pediatric Study Plan
PVP	Pharmacovigilance Plan
RDT	Rapid Diagnostic Test
REMS	risk evaluation and mitigation strategy
RMS/BLA	regulatory management system for the biologics license application
RR	Relative Risk
SAE	serious adverse event
SEP	Surveillance Extension Phase
VCD	Virologically Confirmed Dengue
YF	Yellow Fever

1. EXECUTIVE SUMMARY

The applicant, Sanofi Pasteur (SP) has submitted BLA 125682/0 to support licensure of Dengvaxia, a live, attenuated, tetravalent, chimeric virus vaccine, containing the replication genes and the capsid gene from the attenuated Yellow Fever (YF) 17D strain virus; and the pre-Membrane (prM) and Envelope (E) genes from each of the four wild type dengue serotypes. Dengvaxia is indicated for the prevention of dengue disease caused by serotypes 1, 2, 3 and 4 in individuals 9 through 16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas. Dengvaxia is not indicated in individuals not previously infected by any dengue virus serotype or for whom this information is unknown. Those not previously infected are at increased risk for severe dengue disease when vaccinated and subsequently infected with dengue virus.

Dengue Disease

Dengue disease burden, as characterized by the World Health Organization (WHO) in 2016, is substantial with an estimated 390 million dengue infections occurring annually worldwide, of which approximately 100 million are associated with clinical manifestations; 500,000 with hospitalization; and 20,000 with death (1). Dengue occurs primarily in South America, Asia, the Indian subcontinent and Africa (2). Dengue is endemic in Puerto Rico, Guam, Samoa, and the U.S. Virgin Islands. There are sporadic outbreaks of Dengue in Hawaii and in several mainland U.S. states (primarily Texas and Florida), however dengue is not considered to be endemic in those states.

Prevention of dengue relies on vector control strategies such as personal protection measures or mosquito control programs. There is no licensed preventive dengue vaccine and there are no effective anti-viral drugs available to treat or to provide prophylaxis against dengue infection.

Dengue disease manifestations range from mild, subclinical disease (up to 60% of all dengue infections); to an acute febrile illness that may be characterized by headaches, rigors, a non-specific erythematous rash and malaise (approximately 30% of all dengue infections); to various degrees of Dengue Hemorrhagic Fever (DHF), classified by the WHO into four degrees of severity and which usually results in hospitalization for supportive therapy (approximately 0.5-2.0% of all dengue clinical cases)(6). Severe/hospitalized dengue disease is not associated with any particular dengue serotype but is strongly associated with a second, heterologous dengue infection. Natural infection with any serotype most often results in lifetime protection from that serotype (3,6).

Dengvaxia Clinical Development program

The clinical development program for Dengvaxia included 23 Phase 1 and Phase 2 studies that established vaccine dosage, numbers of doses in the full vaccination series and intervals between doses. A three-dose series {at a dose of 5.0 to 6.0 log10 cell-culture infectious dose 50% ($CCID_{50}$) of each live, attenuated, recombinant, dengue serotype 1, 2, 3, 4 viruses}, at D0, M6, and M12 was determined to be immunogenic and was used in the three clinical disease endpoint efficacy studies that were submitted as the primary basis for licensure (CYD15, CYD14 and CYD23). Study sites were in two major dengue endemic regions (i.e., South America and Asia) and included a total of 10 countries.

CYD15, CYD14, and CYD23 included a combined enrollment of 35,154 subjects randomized 2:1 to receive either Dengvaxia vaccine or placebo control. The same primary efficacy endpoint, i.e., two consecutive days of fever at a temperature ≥ 38°C and virologic confirmation

of any dengue case was used in these studies. Prevention of dengue disease due to any serotype was chosen as a primary endpoint rather than serotype specific prevention of dengue disease because the four dengue serotypes circulate in unpredictable patterns and vary by region, country and year,

CYD15 and CYD14 were Phase 3 studies and were identical in study design. The phase 2 study, CYD 23, was similar to CYD15 and CYD14, although the endpoint was defined as one day of fever at a temperature ≥ 37.5°C and virologic confirmation of any dengue case.

Efficacy Results: Efficacy results were assessed in study CYD 15 (9-16 years, South America, N=20,875); study CYD 14 (2-14 years, Asia, N=10,277); and study CYD23 (4-11 years, Thailand, N=4,002). The per-protocol definition of a dengue case in the two Phase 3 studies was symptomatic, VCD cases occurring during the time of > 28 days after Dose 3 for a period of 12 months and defined as acute febrile illness (temperature ≥ 38°C on at least 2 consecutive days), virologically confirmed by serum RT-PCR for dengue virus and/or dengue nonstructural protein 1 Antigen ELISA (NS1 ELISA).

The pre-specified success criterion for CYD15 and CYD14 was a lower bound (LB) of the 95% confidence interval (CI) of >25%. The pre-specified success criterion for vaccine efficacy (VE) was met, based on the Per Protocol Set for Efficacy (PPSE), with an absolute VE of 60.8% (95% CI: 52.0; 68.0) and 56.5% (95% CI: 43.8; 66.4) for CYD 15 and CYD 14, respectively. **I**n the Phase 2 trial CYD 23, the success criterion was a LB of ≥0 for the 95% CI and the estimated VE was 30.2% (95%CI: -13.4; 56.6), thus the prespecified success criterion was not met.

Immune responses varied as a function of dengue serostatus at baseline with substantially higher GMTs observed pre- and post-vaccination in subjects who were dengue seropositive pre-vaccination compared with those who were not. In the clinical endpoint efficacy trials, a specific $PRNT_{50}$ titer above which VE could be predicted reliably was not identified for any dengue serotype, although neutralizing antibody titers tended to be higher in non-cases than in cases.

Safety Results: There were 4,373 subjects 9 through 45 years of age (3,067, 9 through 16 years of age, and 1,306, 18 through 45 years of age) in the safety data base for reactogenicity. Local and systemic reactogenicity was comparable across studies and in pooled analyses. For CYD15 (the largest clinical endpoint efficacy study conducted in the indicated age range of 9 through 16 years of age) the most commonly reported events (>10% frequency) were: Headache (54.7% versus 57.5% of subjects in Dengvaxia and placebo groups, respectively), pain (48.9% versus 41.0% of subjects in Dengvaxia and placebo groups, respectively), myalgia I fixed it. It had been 17. (43.4% versus 40.5% of subjects in Dengvaxia and placebo groups, respectively), malaise, (40.4% versus 39.6% of subjects in Dengvaxia and placebo groups, respectively), asthenia (37.3% versus 38.1% of subjects in Dengvaxia and placebo groups, respectively), and fever (16.7% versus 18.8% of subjects in Dengvaxia and placebo groups, respectively). Grade 3 reactions were fairly balanced as well (14.7 % versus 11.5% of subjects in Dengvaxia and placebo groups, respectively).

Of the 11 deaths in the Dengvaxia group and 11 deaths in the Placebo group observed in the Active Phase for studies CYD15, CYD14 and CYD23, none were considered by the applicant or the clinical review team to be attributable to vaccination. The percentage of any SAEs within 28 days of vaccine administration that were not severe dengue was similar between Dengvaxia (0.6%) and placebo (0.7%) groups in children 9 through 16 years of age (data from the integrated summary of safety). There were six cases of serious but non-fatal adverse events attributable to Dengvaxia in the pooled analysis of safety data from CYD 14 + CYD15: acute

polyneuropathy; asthma attack; allergic urticarial reaction; unspecified seizures; angioedema with generalized urticarial; and ADEM (acute demyelinating encephalo-myelitis). All subjects recovered completely. Viscerotropic and neurotropic disease were monitored and there were no cases of either in any of the three clinical endpoint efficacy studies.

Cases of severe/hospitalized dengue were considered SAEs. In studies CYD14, CYD15, and CYD23, subjects 9-16 years of age who were dengue seronegative at baseline had a combined relative risk (RR) for severe/hospitalized dengue of 6.25 (95% CI: 0.81; 48.32) whereas the RR for severe/hospitalized dengue in dengue seropositive subjects was 0.18 (95% CI: 0.09; 0.37) and evaluated 28 days post-dose 3 (months 13) to approximately month 66. The observation of this increased RR for severe/hospitalized dengue in dengue seronegative subjects who received Dengvaxia led to the limitation of the indication statement in the prescribing information for Dengvaxia to include only individuals with laboratory-confirmed prior dengue infection.

Advisory Committee:
A Vaccines and Related Biological Products Advisory Committee (VRBPAC) was convened on March 7, 2019 and voted affirmatively that the data submitted to the BLA supported the safety and effectiveness of Dengvaxia in individuals 9 through 16 years of age, residing in dengue endemic regions who had laboratory confirmation of a previous dengue infection. Some committee members expressed concerns regarding inferring vaccine effectiveness in persons 17 – 45 years of age based on pediatric efficacy data and immunogenicity data in adults that were derived from small studies and from persons residing in countries with high dengue endemicity, i.e., Vietnam and India. In addition, there was concern that these data may not be representative of immune responses in subjects living in Puerto Rico. Of note, the applicant initially requested an indication for individuals 9 through 45 years of age with the Biological License Application (BLA) submitted on August 31, 2018. Following post-VRBPAC discussions with CBER, the applicant requested on April 1, 2019 to limit the age indication to 9 through 16 years of age.

Because data intended to support safety and immunogenicity of Dengvaxia in adults ages 18 through 45 were submitted to the BLA, they were reviewed and are described in this memo, however, they were not considered central to the assessment of safety and effectiveness for the currently proposed age indication of 9 through 16 years of age.

Pediatric Research Equity Act (PREA):
The Pediatric Study Plan (PSP) included a waiver for individuals from birth to < six months of age because studies are impossible or highly impractical (i.e., the number of pediatric patients who would be both infected with Dengue and have laboratory confirmation of the infection is small and geographically dispersed). A deferral for six months to <2 years of age was granted until additional safety and effectiveness data will have been collected in older children. A deferral for 2 to <9 years was granted because the biological product is ready for approval for use in adults before pediatric studies are completed.

Pharmacovigilance Plan (PVP) and Post Marketing Studies:
The applicant submitted a PVP which includes a pregnancy registry; surveillance for occurrence of clinically severe dengue in persons who have been vaccinated with Dengvaxia; and surveillance for occurrence of acute, severe hypersensitivity reactions.

Risk-Benefit Analysis and Summary Recommendations:
There is a substantial unmet medical need for prevention of both dengue disease and severe dengue disease. There are no available anti-viral drugs to treat dengue infections and vector

control strategies are impeded by the biting and living habits of the dengue vectors (*Aedes egypti and Aedes albopticus*). A dengue vaccine of even modest effectiveness could afford a substantial benefit of reduction of any dengue and severe dengue cases.

In subjects dengue seropositive pre-vaccination, the vaccine demonstrated efficacy against VCD, induced substantial antibody responses, and was associated with a substantial reduction in the RR for severe/hospitalized dengue disease post-vaccination. Conversely, subjects who were dengue seronegative pre-vaccination demonstrated lower VE against VCD, lower immune responses, and had an increased RR for severe dengue disease post-vaccination. Given these findings, the indication for Dengvaxia is limited to subjects 9-16 years of age with laboratory confirmed previous dengue infection and living in endemic areas. In addition, the prescribing information will include a Limitations of use statement that Dengvaxia is not approved for use in individuals not previously infected by any dengue vaccine serotype or for whom this information is unknown.

CBER recommends approval of Dengvaxia for persons 9 through 16 years of age, residing in dengue endemic regions, and who have laboratory confirmation of a previous dengue infection.

1.1 Demographic Information: Subgroup Demographics and Analysis Summary

The two Phase 3 clinical efficacy studies (CYD15 and CYD14) and the one Phase 2 efficacy study (CYD23) were conducted outside the United States mainland. Puerto Rico, a U.S. territory, was included in CYD15 because dengue is not endemic in mainland U.S.

Subgroup analyses were conducted by age and showed that vaccine immunogenicity and efficacy varied as a function of age with younger age subgroups (2-5 years and 6-11 years) having lower, 28-day post-injection 3 GMTs and lower efficacy against any dengue case compared to older subgroup (9-16 years).

There was a mild (6-8%) difference in VE as a function of sex, with females having lower efficacy than males. BMI also affected vaccine efficacy with higher BMI subjects having a 4-6% lower vaccine efficacy compared to lower BMI subjects.

Race and ethnicity were not evaluated as factors that could impact effectiveness. CYD15 was conducted in five South American countries where the majority of subjects identified as “Hispanic” and CYD14 and CYD23 were conducted in five Asia Pacific countries where the clear majority of subjects identified as “Asian”.

1.2 Patient Experience Data

No patient experience data were submitted to the BLA, as noted in Table 1 below.

Table 1. Patient Experience Data Relevant to this Application

☐	The patient experience data that was submitted as part of the application include:			Section where discussed, if applicable
	☐	Clinical outcome assessment (COA) data, such as		[e.g., Sec 6.1 Study endpoints]
		☐	Patient reported outcome (PRO)	
		☐	Observer reported outcome (ObsRO)	
		☐	Clinician reported outcome (ClinRO)	
		☐	Performance outcome (PerfO)	
	☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		[e.g., Sec 2.1 Analysis of Condition]
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify)		
☐	Patient experience data that were not submitted in the application, but were considered in this review			
		☐	Input informed from participation in meetings with patient stakeholders	
		☐	Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
		☐	Observational survey studies designed to capture patient experience data	
		☐	Other: (Please specify)	
☒	Patient experience data was not submitted as part of this application.			

2. CLINICAL AND REGULATORY BACKGROUND

2.1 Disease or Health-Related Condition(s) Studied

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). In the past 40 years there has been a substantial increase in the numbers of countries where dengue is endemic; in general, all four dengue serotypes are identified each year in most countries although one or two dengue serotypes usually are dominant. However, dengue attack rates and dengue sero-prevalence vary substantially within countries, therefore the use of a

country-wide seroprevalence rate to estimate the likelihood of any given person being seropositive pre-vaccination is limited. Dengue is considered endemic in Puerto Rico, 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 and in Hawaii (2). Furthermore, dengue vectors are found in many states in the U.S. where dengue is not currently endemic, thus posing a potential future threat for dengue endemicity given the proper conditions.

Dengue Infection and Disease

Dengue infection occurs when the bite of a competent vector (*Aedes aegypti* mosquito or *Aedes albopictus* mosquito) injects the dengue virus into the extravascular tissue and the virus infects primarily dendritic cells, after which the draining lymph nodes become infected and subsequently the individual becomes viremic for a period of 3-5 days during which the acute febrile illness may be manifested. Dengue disease manifests across a spectrum of clinical illness ranging from asymptomatic (up to 60%) to a non-specific, febrile, viral syndrome to severe, fatal hemorrhagic disease.

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.,6.).

Approximately 95% of DHF cases occur with a second dengue infection, which is almost always from a heterologous serotype. Although the mechanism(s) leading to DHF is unclear, Antibody Dependent Enhancement (ADE) is thought to play an important role. Initial infection by any of the four dengue serotypes induces potent humoral and cellular immune responses that generally prevent a second infection by the same serotype. However, primary dengue infections may also induce broadly cross-reactive but weakly binding antibodies against heterologous serotypes, that upon a secondary, heterologous dengue infection, can trigger ADE with resultant DHF (2;5).

Laboratory Testing for Dengue

In a symptomatic individual, dengue disease can be confirmed by evaluating for presence of viral antigen or viral replication by nucleic acid amplification testing. Dengue virus can be detected for 5-7 days after symptom onset using the following current methodologies:

- RT-PCR for presence of dengue virus nucleic acids from body or blood tissues (serum, plasma, blood, cerebrospinal fluid),
- ELISA dengue NS1 antigen (serum), and
- cell culture of dengue virus from serum, plasma, cerebrospinal fluid.

Serologic confirmation of a suspected dengue virus case can be performed by any of the following methods:

- Detection of anti-DENV IgM by a validated immunoassay in serum or CSF specimen in a person living in a dengue endemic or non-endemic area of the US without evidence of other flavivirus transmission
- Detection of anti-DENV IgM in a serum or CSF specimen in a traveler returning from a dengue endemic area without ongoing transmission of another flavivirus, clinical evidence of co-infection with another flavivirus, or recent vaccination against a flavivirus

- Anti-DENV IgM seroconversion by validated immunoassay in acute (collected < 5 days of illness onset) and convalescent (collected > 5 days after illness onset); or
- IgG anti-DENV seroconversion or ≥ 4-fold rise in titer by a validated immunoassay in serum specimens collected > 2 weeks apart, and confirmed by a neutralization test

2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)

In the U.S., there are no approved antiviral treatments for dengue. There is no current, U.S. licensed dengue vaccine. 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 are limited to personal protection from mosquito bites and vector control strategies, neither of which has been shown to significantly reduce dengue disease burden in endemic regions.

2.3 Safety and Efficacy of Pharmacologically Related Products

At present, there is no licensed dengue vaccine in the United States (US).

2.4 Previous Human Experience with the Product (Including Foreign Experience)

Dengvaxia has been licensed in 21 countries, although in 2018 Malaysia declined to renew a two-year provisional license and the Philippines revoked the license as of February 2019. Approximately 2.9 million doses of Dengvaxia have been distributed, and approximately 950,000 individuals have received a three-dose series. Most vaccine recipients were 9-16 years of age. Prescribing information for Dengvaxia in countries outside the US has not included a limitation of the indication to individuals with laboratory evidence of previous dengue infection, although the European Medicine Agency (EMA) does recommend this limitation. The applicant is reported to have a global risk management plan in place to continuously evaluate the risks and benefits of Dengvaxia outside the US. This includes both active and passive surveillance (routine and enhanced safety surveillance measures as well as ongoing safety studies). Of the 2.9 million distributed doses, there have been 2992 spontaneous case reports including 553 serious adverse events (SAEs), most of which were consistent with the adverse events (AEs) observed in the clinical development program. Allergic and anaphylactic reactions were rare (<0.01%). Three cases of anaphylactic reactions were reported (estimated to be 1 case per million doses distributed). An increased risk of severe, hospitalized dengue in individuals who have not had a prior dengue infection was observed during the clinical development of Dengvaxia (see Section 8, Integrated Summary of Safety). During post-marketing surveillance, the applicant reported a total of 151 cases of dengue that occurred post-vaccination; 110 were reported as severe or hospitalized dengue of which 51 were virologically confirmed (Dengvaxia VRBPAC briefing document, Sanofi Pasteur, Version 1.0 dated February 4, 2019, page 139). In most cases there was limited information about medical history. Since dengue disease was endemic in regions where patients were vaccinated, cases of breakthrough dengue of varying degrees of severity may be expected. Whether severe cases were a result of incomplete schedule, vaccine failure, or increased risk of severe dengue in persons vaccinated who had no previous dengue infection is unknown.

Clinical Reviewer Comment: *Approximately 950,000 individuals, mainly in the age range of 9-16 years, have received the full three-dose series of Dengvaxia in dengue-endemic countries. Individuals were vaccinated without the limitation of vaccination of a laboratory-confirmed prior dengue infection, therefore the relative risk (RR) for severe dengue post-vaccination in*

individuals without laboratory confirmed previous dengue infection in post-licensing surveillance cannot be determined.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission

The following list includes references to selected submissions to Center for Biologics Evaluation and Research (CBER), important protocol amendments, discussions between CBER and the applicant that reflected either the applicant's or CBER's thinking about the clinical development plan, as well as regulatory activities that were milestones.

15 AUG 2003: The applicant submitted an IND to CBER for Dengue Virus Tetravalent (Serotype 1, 2, 3, 4) Chimeric Yellow Fever Virus (strain 17D with pre-M and E dengue constructs) Vaccine (Vero cell), Live

09 NOV 2009: A Type C Meeting was held to discuss the applicant's clinical development plan and approach for submission of phase 3 efficacy studies.

18 JUN 2010: A request for Fast Track Designation was granted.

07 DEC 2010: A Type C Meeting was held to discuss the applicant's plans to conduct phase 3 clinical trials. CBER and the applicant agreed on criteria for a dengue case definition. CBER recommended that the hospitalization phase (HP) be extended 1 year for a total of 5 years study duration to further evaluate of the risk for severe dengue post-vaccination, to which the applicant agreed.

04 NOV 2013: A Type B End-of-Phase 2 meeting was held to discuss the design of the proposed phase 3 studies. The applicant and CBER agreed that the proposed phase 3 studies for Dengvaxia should include one year of active phase follow up data and at least three years of HP follow up data.

16 JUN 2014: Amendment 194 contains the agreed initial Pediatric Study Plan (iPSP). The PeRC agreed with the applicant's plan for an assessment of children 2 through 16 years of age, deferral of the requirement for pediatric assessments for children 2 months to 23 months of age and to request a waiver of the requirement for pediatric assessments for children 0 to 2 months of age on 09 JUL 2014. The applicant was notified that the iPSP was acceptable in a letter dated 15 JUL 2014.

09 DEC 2014: A Type C meeting was held to discuss the results of the CYD14 and CYD15 clinical trials which included 1 year of active phase follow up and 1 year of HP follow up data. An imbalance of severe dengue cases in subjects who received Dengvaxia and had subsequent exposure to dengue was identified and discussed at this meeting. The applicant discussed that the reason for the imbalance in severe dengue cases was not clear at that time, although it correlated with age (i.e. the imbalance was more pronounced in children younger than 9 years of age). CBER discussed that they were concerned that the imbalance could be due to the subject's dengue serostatus at the time of vaccination and that subjects who were seronegative were more likely to be predisposed to severe dengue after vaccination. CBER indicated that understanding the observed imbalance in severe dengue cases would be an important concern to address with an original biologics license application (BLA) is submission.

15 JAN 2016: A technical working group meeting was held to discuss the immunogenicity results of CYD14 and CYD15 and the applicant's work on identifying a correlate of protection.

The applicant was not able to determine a value from their immunogenicity data that could be considered a threshold for vaccine effectiveness (VE).

05 APR 2016: A Type C meeting was held to discuss the applicant's comparability studies on working seed lots. In general, CBER agreed with the applicant's approach for assessing lot to lot comparability between three Phase 3 lots and between Phase 2 and Phase 3 lots.

11 JUL 2016: A Type C meeting was held to discuss the clinical development plan and what data would be BLA would contain. The applicant proposed that the age indication for Dengvaxia would be for individuals 9 years through 45 years of age. The previous proposed indication was for individuals (b) (4) years of age. The request to increase the lower bound of the requested age range from (b) (4) to 9 years of age was based on the increased RR for severe/hospitalized dengue in subjects who were dengue seronegative pre-vaccination, given the relationship between younger age and a higher likelihood of having had no prior dengue infection. The request to lower the upper bound of the age range from (b) (4) years of age was due to the lack of safety and immunogenicity data for individuals in this age group.

29 SEP 2016: A Type B pre-BLA meeting was held to discuss the proposed Chemistry Manufacturing and Controls (CMC) package to be submitted to support licensure of Dengvaxia and the manufacturing facilities.

01 NOV 2016: A Type B pre-BLA meeting was held to discuss the proposed clinical package to be submitted to support licensure of Dengvaxia.

21 DEC 2016: The applicant 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 applicant on 01Feb 2017 for dataset formatting and compilation (125645/0.2).

01 NOV 2017: A technical working group meeting was held to discuss the results of the applicant's NS1 Ag ELISA. The NS1 Ag ELISA was conducted on samples collected 28 days post-dose 3 (i.e., month 13) to understand study subjects' dengue serostatus at baseline because per protocol on approximately 10% of subjects had baseline serum collection for the purpose of secondary immunogenicity analyses. The results of the NS1 Ag ELISA were used to further assess the safety and effectiveness of Dengvaxia relative to pre-vaccination dengue serostatus. The major conclusion from the meeting was that there was an increased RR of severe/hospitalized dengue in subjects who were seronegative for dengue by NS1 Ag ELISA who received Dengvaxia and were subsequently infected with dengue compared to those who were seronegative for dengue and received placebo.

31 MAY 2018: A Type B pre-BLA meeting was held to discuss the manufacturing facilities, the clinical datasets to be submitted in support licensure of Dengvaxia, and the pharmacovigilance studies to be conducted post licensure.

31 AUG 2018: BLA submission received through FDA gateway.

07 MAR 2019: A VRBPAC meeting was held on this date. Advisory committee members were asked to consider the safety and effectiveness data submitted in support of the requested indication for the age range of 9 through 45 years of age. The committee voted in favor of safety

and effectiveness in 9 through 16 years but voted that the effectiveness data did not support the approval of Dengvaxia in individuals 17 through 45 years and rendered a tied decision on safety in that age group. (Please see Section 5.4.1 for further details).

01 April 2019: The applicant notified CBER that they wanted to change their requested indication to 9 through 16 years of age.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The application was adequately organized and integrated to accommodate the conduct of a complete clinical review.

3.2 Compliance With Good Clinical Practices And Submission Integrity

The studies submitted in support of this application were conducted in compliance with Good Clinical Practices.

3.3 Financial Disclosures

Table 2 reports shows that none of the investigators had financial conflicts of interest to disclose.

Table 2. Financial Disclosures for Investigators participating in Studies Submitted to This BLA

Covered clinical study (name and/or number):All studies reviewed in Clinical Review		
Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from applicant)
Total number of investigators identified: >100		
Number of investigators who are sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		

Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) _____		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from applicant)

4. SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES

4.1 Chemistry, Manufacturing, and Controls

The CMC review concurred with the assay validations, manufacturing controls and final lot release specifications for Dengvaxia. End-expiry potency specification is (b) (4) Log $_{10}$ CCID$_{50}$ for each serotype and minimum lot release potency specification is (b) (4) Log$_{10}$ CCID$_{50}$ for each serotype. Dengvaxia should be administered within 30 minutes of reconstitution. The potency specifications were based upon the immunogenicity responses and efficacy results observed in the two Phase 3 efficacy endpoint trials. Please see the CMC review for details.

4.2 Assay Validation

Please see the CMC review.

4.3 Nonclinical Pharmacology/Toxicology

Please refer to the Toxicology & CMC reviewers for details. For the nonclinical safety evaluation the Dengvaxia vaccine was evaluated in a general repeat dose toxicity study in monkeys, distribution, persistence and shedding studies (reviewed by the CMC reviewer); studies evaluating the viscerotropism, neurotropism and neurovirulence (reviewed by the CMC reviewer) as well as developmental and reproductive toxicity (DART) studies which included two immunogenicity/viremia studies, two investigational and two pivotal reproductive developmental toxicity studies in mice and rabbits as well as a lactation study in mice. In monkeys, the vaccine was well tolerated, and no vaccine related systemic or local toxicities were identified. In the immunogenicity/viremia studies and the investigative, preliminary dose-ranging data, the rabbit and the mouse were confirmed as models for DART studies with a robust antibody response in the rabbit and detectable viremia in the mouse after intravenous administration.

In the rabbit studies, no indication of maternal systemic toxicity, no test article- effects on mating performance and fertility, and no indication of teratogenic potential of the test vaccine as well as no effect on pre and post-natal development of the pups were reported when a full human dose was administered twice before mating and three times during gestation. The mouse was selected to investigate the exposure to the virus after one IV injections at a dose of 5 (one full human dose), 6.5 or 8 log10 CCID$_{50}$ on GD 6, 9 or 12. The doses of 6.5 and 8 log$_{10}$ CCID$_{50}$ induced reductions in maternal body weight gains and food consumption and increases in post-implantation loss. The most pronounced effects occurred in females given 8 log10 CCID$_{50}$ on DG 9 and were associated with reduced fetal body weights in litters of females given 8 log10 CCID$_{50}$ on DG 9 or 12. Changes at the fetal examination were limited to delays in skeletal ossification at 6.5 or 8 log10 CCID$_{50}$ of Dengvaxia where reductions in the fetal body weights

and maternal toxicity occurred, but no fetal abnormalities. At 5 log10 $CCID_{50}$ Dengvaxia, there were no changes of toxicological significance. In rabbits given the high dose by the intravenous (IV) route, viremia was detected at a low level on the day after the injection. In the mice, viremia was detected on the day of the injection (+ 7 hours) and during two days after injection in mice given the high dose by the IV route.

Dengvaxia centrations of 5, 6.5 and 8 log10 $CCID_{50}$ did not induce vaccine-related embryo-fetal development effects in (b) (4) female rabbits. No indication of maternal systemic toxicity was reported in the mice Developmental and Reproductive Toxicity Study in (b) (4) Rabbits Following Repeated Intravenous Administrations, no test article-effects on mating performance and fertility, and no indication of teratogenic potential of the test vaccine as no effect on pre and post-natal development of the pups were reported.

Clinical Reviewer Comment: *The monkey, mice and rabbit studies did not appear to reveal important toxological concerns, including those on fetal development. In animal studies evaluating intravenous administration of Dengvaxia viremia was noted to be at low levels and of short duration.There was no significant viral shedding. There was no evidence of neurotropic or viscerotropic adverse events. The observed effects of reduced maternal body weight and post-implantation loss in the mouse studies were not considered to be predictive of potential human toxicity because of the I.V. route of administration and the 100-1,000 times human dose given.*

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Dengvaxia contains live attenuated viruses. Following administration, the attenuated viruses are thought to elicit neutralizing antibodies and cell-mediated immune responses against the four dengue virus serotypes. The mechanism of action is unknown.

4.5 Statistical

The Statistical Analysis Plans for each study reviewed were considered by the biostatistics reviewer to be appropriate for the study design and endpoints assessed in the study. Details of each statistical analysis plan are provided under each study section, Sections 6.1 to 6.4. Please refer to the statistical review for comprehensive comments. The statistical review made the following summary conclusions:

1. Overall, it was determined that the totality of the data from the studies that were intended to serve as the primary basis for licensure (i.e., studies CYD15, CYD14, and CYD23) demonstrated substantial evidence of effectiveness, based on their pre-specified efficacy objectives, endpoints and associated success criteria.
2. The reduction of VCD incidences post-dose 3 and during the Active Phase of surveillance was observed for all four dengue serotypes. For serotype 1 and serotype 2, however, there was, in general, lower VE compared to serotypes 3 and 4.
3. The VEs were, overall, were numerically higher in baseline dengue seropositive subjects compared to the baseline dengue seronegative subjects.
4. The Dengvaxia vaccine reduced hospitalized VCD cases by 78.6% (95% CI: 57; 90) in post-dose 3 period and 80.3% (95% CI: 65.0; 89) in Active Phase, in CYD15. In CYD14, these respective VEs were 71.4% (95% CI: 49;84) and 67% (95% CI: 50;79). Reduction was also seen in VCD cases meeting WHO criteria, with VE ≥ 80% regardless of periods and in both pivotal studies.
5. Estimates of VE against VCD post dose 3 varied by subject age, with the lowest estimated VE of 45.7% (95% CI: 17.2;64.3) observed in subjects 2-5 years of age

(Study CYD14) and an estimated VE of 56.2% (95% CI: 45.9; 64.5) and 68.7% (95% CI: 59.1;76.0), at 6-11 years of age and 12-16 years of age, respectively from integrated results of studies CYD\14 and CYD15.

4.6 Pharmacovigilance

Please see the Pharmacovigilance Plan (PVP) review. The Office of Biostatics and Epidemiology (OBE), in the PVP review, characterized the plan as "routine pharmacovigilance". The applicant proposed the following global post-marketing monitoring plan to further evaluate vaccine safety and effectiveness and mitigate important identified risks:

- completion of CYD14 and CYD15 (long term safety and efficacy data),
- routine monitoring of spontaneous reports from internal and external databases as well as monitoring of vaccine exposure and data,
- enhanced safety surveillance measures to document AESIs through specific questionnaires in case of dengue or allergic reactions,
- non-interventional post-authorization effectiveness studies and post-authorization safety studies in different endemic countries (study DNG11; DNG15),
- a pregnancy registry,
- post-authorization effectiveness studies, and
- a healthcare provider (HCP) guide to educate providers on increased risk of hospitalized and severe VCD in individuals not previously infected.

Clinical Reviewer Comment: *Dengvaxia vaccination has an observed effect of being associated with an increased RR of severe dengue post-vaccination in persons who are dengue seronegative at baseline, pre-vaccination. Although the requested indication for this vaccine for U.S. licensure includes the limitation of having a laboratory-confirmed prior dengue infection, there is some uncertainty about the performance characteristics of the available serological tests in the dengue endemic territories of the U.S. There is a risk of a false-positive test for dengue in the context of other flaviviruses and there are no currently available rapid diagnostic tests (RDTs) that have been evaluated by FDA standards. Given these considerations, there is some risk of vaccination of persons who have not had previous dengue infection, and the proposed PVP does not directly address this risk nor provide a means for assessing this risk post-licensure. Although the PVP includes an HCP guide to educate HCP's about risks of vaccination of persons who do not have laboratory confirmation of a previous dengue infection, and the PVP provides for enhanced surveillance of clinically severe dengue cases post-vaccination, there is no mechanism proposed to link a case of severe dengue post-vaccination with the primary health care vaccination record and the assessment of previous dengue infection. However, consideration of Dengvaxia effectiveness in preventing dengue cases of any serotype and in lowering the risk for severe dengue post-vaccination in individuals with laboratory confirmation of a previous dengue infection pre-vaccination led to the conclusion that Dengvaxia would have a substantial benefit on a population basis in dengue endemic areas.*

5. SOURCES OF CLINICAL DATA AND OTHER INFORMATION CONSIDERED IN THE REVIEW

5.1 Review Strategy

The review strategy was influenced by the indication sought for Dengvaxia at the time of the BLA submission on 31 August 2018; for 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.

Efficacy, immunogenicity, and safety data in support of this application were provided from three studies that had the identical clinical efficacy endpoint of VCD cases of any serotype. Two of these studies were phase 3 (CYD15 and CYD14) and one was a phase 2 study (CYD23). Each of these studies are reviewed separately (Sections 6.1, 6.2 and 6.3) in this clinical review because they inform the effectiveness of the product in different regions of the world and differed for the predominant dengue serotype circulating during the study period. These factors warranted an independent review of each study because safety, effectiveness, and immunogenicity appeared influenced by age, by dengue serostatus of subjects at baseline, as well as by dengue epidemiology in different countries and regions of the world.

Section 6.4 describes study CYD17 because this study supported manufacturing consistency and bridging of phase 3 lots to the clinical lots used in the studies CYD15, CYD14, and CYD23

Studies CYD22, CYD28 and CYD47) were submitted to the BLA to support and age indication for individuals 18 through 45-year age group. Based on the sponsor's subsequent request to limit the age indication to individuals 9 through 16 years of age, these data were no longer considered central to the review and therefore the study designs and data were briefly summarized Section 9.2.2 Aspects of the Clinical Evaluation no Previously Covered.

5.2 BLA/IND Documents That Serve as the Basis for the Clinical Review

The following BLA documents served as the basis for the clinical review:

eCTD Module 1: 1.9.1 Request for Waiver of Pediatric Studies; 1.9.2 Request for Deferral of Pediatric Studies; 1.14.1 Draft Labeling and 1.16 Risk Management Plan

eCTD Module 2: 2.5 Clinical Overview 2.7 Clinical Summary

eCTD Module 5: Clinical Study Reports for Studies CYD15, 14, 23, 22, 28, 47, 17.

5.3 Table of Studies/Clinical Trials

Table 3 lists all the studies undertaken in the clinical development plan for this CYD vaccine that were reviewed in this clinical review.

Table 3. Overview of Selected Clinical Studies Submitted to the Dengvaxia BLA STN 125682/0

Study	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

Study	Study Design (Phase)	Main Objectives	Sample size and dosing regimen	Age range	Countries (endemicity)
					(dengue - endemic)
CYD23	Like CYD15 - differences highlighted where important (phase IIb)	Like 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)
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])	2-45 years	Vietnam (dengue-endemic)

Study	Study Design (Phase)	Main Objectives	Sample size and dosing regimen	Age range	Countries (endemicity)
			Control[5]: (n = 60 [10 adults; 50 adolescents and children])		
CYD 17	Phase III, randomized, placebo-controlled, blind-observer, multicenter trial.	Lot-to-lot consistency across 3 Phase III lots. - Bridging between Phase II and Phase III lots. - Descriptive safety, after each injection	Randomized: 715 - Group 1: 164 - Group 2: 163 - Group 3: 163 - Group 4: 168 - Group 5: 57	18-60 years	Australia

[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 0.9%) 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.
Source: Adapted from STN 125682/0, Tabular Listing of Clinical Studies

5.4.1 Advisory Committee Meeting

A VRBPAC meeting was convened on 7 March 2019 to consider the safety and effectiveness data submitted in support of the requested indication for the age range of 9 through 45 years. The committee voted in favor of safety and effectiveness of Dengvaxia in individuals 9 through 16 years of age. The committee voted that the data did not support the effectiveness of Dengvaxia in individuals 17 through 45 years of age and rendered a tied decision on safety in that age group. The committee expressed concerns about whether the available immunogenicity data in adults 18 through 45 years were adequate to support the assertion that Dengvaxia is effective in this age range. These concerns were:

- the small number of subjects evaluated in CYD22, CYD47 and CYD28 (a total of 170-194 subjects who were dengue seropositive pre-vaccination);
- the post-dose 3 GMTs from CYD28 in Singapore which were lower than the post-dose 3 GMTs in CYD14 and CYD15 at least in part due to lower pre-vaccination GMTs in Singapore;
- use of descriptive immunogenicity analyses of the GMTs in adults instead of pre-specified endpoints and success criteria for the comparison of GMTs in adults to those in adolescents; and
- the lack of data on adult immune responses from Puerto Rico which is the US territory where Dengvaxia is likely to have the most uptake.

In its deliberations the committee considered the epidemiology of dengue disease in Puerto Rico. The committee agreed that data support the effectiveness of Dengvaxia in pediatric subjects with prior exposure to dengue virus and living in endemic areas. The Committee expressed concern about the safety signal identified in the clinical-endpoint efficacy studies

(CYD15, CYD14, and CYD23), namely an increased risk of hospitalized and severe dengue in individuals with no prior exposure to dengue who were vaccinated with Dengvaxia and subsequently infected with dengue. There was consensus that the dengue serostatus of individuals would need to be determined prior to vaccination if the vaccine were licensed and recommended for use and the individual did not have a medical record of a laboratory-confirmed previous dengue infection. Concern was expressed that currently available serological tests to establish previous dengue infection may lead to false positive results because of cross-reactivity with other flaviviruses. The committee also noted the operational, logistical, and infrastructural concerns of serotesting prior to vaccination. There was broad recognition of the value of an FDA cleared rapid diagnostic assay to establish prior exposure to dengue in individuals to be vaccinated.

Clinical Reviewer Comment: *Subsequent to the recommendations provided by the VRBPAC, the applicant notified CBER on 1 April 2019 of a change in requested indication, limiting the age indication to 9 through 16 years and individuals who have laboratory confirmation of a prior dengue infection and reside in dengue endemic regions.*

5.5 Literature Reviewed

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6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1: CYD15

Study title: Efficacy and Safety of a Novel Tetravalent Dengue Vaccine in Healthy Children and Adolescents Aged 9 to 16 years in Latin America (NCT 01374516)

Study start date: June 8, 2011 Study completion date: April 21, 2018.

CYD15 was a phase 3 clinical endpoint efficacy trial conducted in four South and Central America countries and Puerto Rico. A total of 20,869 subjects 9-16 years old were enrolled and randomized in a 2:1 ratio (Dengvaxia vaccine: placebo [normal saline]). CBER agreed that data in support of safety and effectiveness from month 0 through month 60 could be submitted with the BLA and data from month 61 through month 72, to further characterize severe, hospitalized

dengue, could be submitted in second quarter of 2019. (Please refer to Section 6.1.2, Design Overview, for clarification of the time line of this trial).

6.1.1 Objectives (Primary and Secondary)

The primary objective was to assess the efficacy of Dengvaxia after 3 vaccinations administered at 0, 6 and 12 months to prevent symptomatic VCD cases, regardless of the severity, due to any of the four serotypes, in children and adolescents 9 through 16 years of age at the time of inclusion. Symptomatic VCD was defined as an acute febrile illness (i.e., temperature ≥ 38°C on at least 2 consecutive days) confirmed by dengue RT-PCR and/or dengue NS1 ELISA Ag test.

Clinical Reviewer Comment: *The case definition for a dengue case due to any serotype required a febrile episode and virological confirmation of the dengue infection by serotype which is consistent with 1997 WHO recommendations for dengue efficacy studies and with which CBER agreed. CBER viewed efficacy against any dengue serotype case to be an acceptable primary objective, acknowledging that serotype-specific efficacy would likely vary between the four serotypes. Dengue viruses circulate in unpredictable patterns each year, by country and by regions within countries, and even though in most dengue endemic countries three or four serotypes circulate simultaneously, there is usually a predominant serotype in any given year. The primary objective and the primary endpoint of efficacy against dengue cases of any serotype was acceptable, based upon the likelihood of clinical benefit and based upon the feasibility of having sufficient cases of any serotype in any country of study.*

Secondary objectives were:

- the occurrence of SAEs, including serious adverse events of special interest (AESIs), in all subjects throughout the trial period, from the date of first injection through the end of the 3-year HP (data submitted in the BLA) and then throughout the surveillance expansion phase (SEP) (final twelve months of data for year six of the Hospital Phase to be submitted in second quarter of 2019);
- to describe the occurrence of hospitalized VCD cases and the occurrence of severe, VCD cases, throughout the 3-year H (data submitted with the BLA) and then the SEP;
- to describe the reactogenicity of Dengvaxia in a subset of participants after each dose; to describe the antibody response to each dengue serotype in a subset after Dose 2, after Dose 3, and 1, 2, 3, 4 and 5 years after Dose 3; and
- to describe the efficacy of Dengvaxia in preventing symptomatic, VCD cases by serotype.

6.1.2 Design Overview

CYD15, was a phase 3, prospective, randomized (2:1 Dengvaxia to Normal Saline Placebo), observer-blinded, multi-center clinical endpoint efficacy study conducted in five countries in South and Central America and in Puerto Rico, in two phases as illustrated in Figure 1. The Active Phase, from M0 to M25 included a 12-month period for injections at M0, M6 and M12, and then a 12-month active case detection period from 28 days post-dose 3 (M13 to M25). The HP was initially from M25 to M60, during which active surveillance for severe/hospitalized dengue cases was conducted. During year 2 of the HP an imbalance of severe/hospitalized cases in the Dengvaxia compared to the placebo group was observed resulting in the following protocol modifications:

- A SEP was added to the trial, which began at the end of Year 4 of the HP and included re-consenting of all willing subjects to participate in the resumption of active case detection for any symptomatic, VCD case (approximately 92% of all subjects were re-consented).

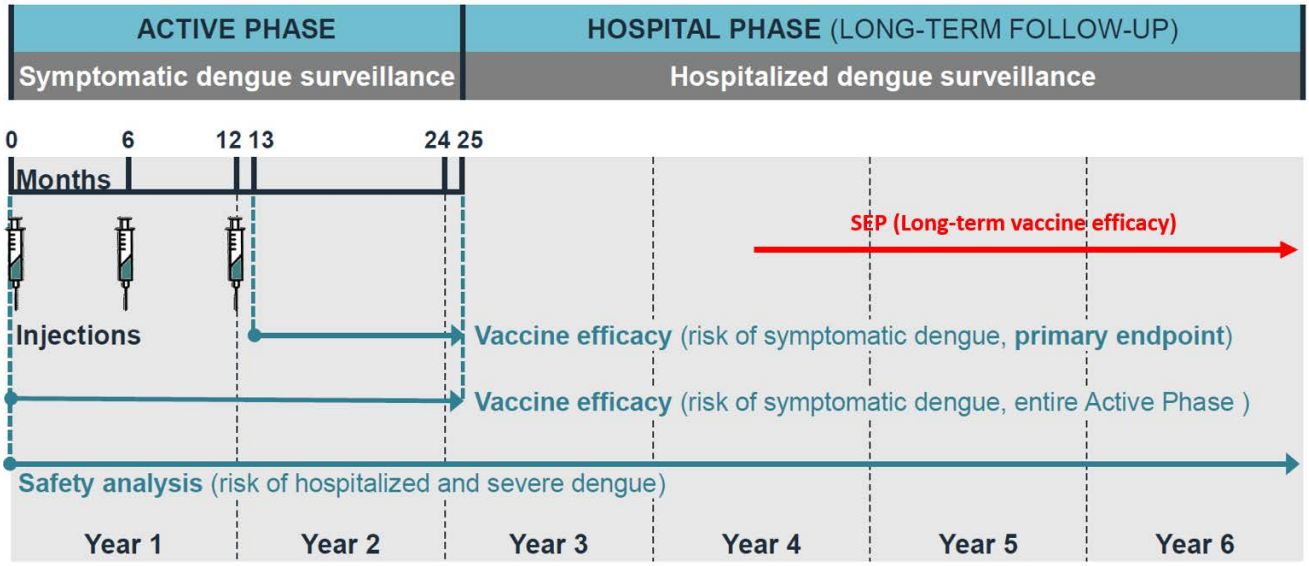
- Blood was collected at the time of re-consenting
- The addition of one more years to the HP. Data included in this submission were for the first 60 months (through year 5) of the trial, which included approximately 14 months of this SEP. Per agreements reached with the applicant, it is anticipated that data from the 6th year of the HP will be submitted in 2nd quarter of 2019.

Clinical Reviewer Comment: *The trial design was adequate for assessing safety and effectiveness of Dengvaxia and the addition of the SEP was appropriate to further clarify the risk of severe/hospitalized dengue cases.*

Figure 1 shows a schematic of the CYD15 study design.

- The Active Phase was from M0 to M25 and included M0 to M12 for the three doses of Dengvaxia or Placebo to be administered at D0, M6 and M12. Active case detection of any dengue case due to any serotype was from 28 days post-dose 3 to M25.
- The HP began at month 26 and extended to M60, during which active surveillance for dengue cases requiring hospitalization was conducted.
- The SEP began at approximately M40 and extends to M72 although data submitted in this application was through M60, with final 12 months of data to be submitted later in 2019. Willing subjects were re-consented at the beginning of the SEP and had a serum sample drawn and both active case detection for dengue cases due to any serotype and active hospital surveillance for any dengue case requiring hospitalization were conducted during the SEP.

Figure 1. Schematic of CYD15 Study Design



Source: Adapted from Hadinegoro et al. (2015) NEJM v273 (13), p1195-120

6.1.3 Population

Inclusion Criteria

- Nine to 16 years of age on the day of inclusion and resident of the site zone
- Subject in good health, based on medical history and physical examination
- Assent form or informed consent form has been signed and dated by the subject (based on local regulations), and informed consent form has been signed and dated by the parent(s) or another legally acceptable representative (and by an independent witness if required by local regulations)
- Subject able to attend all scheduled visits and to comply with all trial procedures

Exclusion Criteria

- Subject is pregnant, or lactating, or of childbearing potential (to be considered of non-childbearing potential, a female must be pre-menarche, surgically sterile, or using an effective method of contraception or abstinence from at least 4 weeks prior to the first vaccination until at least 4 weeks after the last vaccination)
- Participation in another clinical trial investigating a vaccine, drug, medical device, or a medical procedure in the 4 weeks preceding the first trial vaccination
- Planned participation in another clinical trial during the present trial period
- Self-reported or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy within the preceding 6 months; or long-term systemic corticosteroids therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months)
- Self-reported seropositivity for Human Immunodeficiency Virus (HIV) infection
- Self-reported systemic hypersensitivity to any of the vaccine components, or history of a life- threatening reaction to the vaccine used in the trial or to a vaccine containing any of the same substances
- Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with trial conduct or completion
- Receipt of blood or blood-derived products in the past 3 months, which might interfere with assessment of the immune response
- Planned receipt of any vaccine in the 4 weeks following any trial vaccination
- Deprived of freedom by administrative or court order, or in an emergency setting, or hospitalized involuntarily
- Current alcohol abuse or drug addiction that may interfere with the subject's ability to comply with trial procedures
- Identified as a site employee of the Investigator or study center, with direct involvement in the proposed study or other studies under the direction of that Investigator or study center, as well as a family member (i.e., immediate, husband, wife and their children, adopted or natural) of the site employees or the Investigator

Clinical Reviewer Comment: *The eligibility criteria were appropriate for an intended population of healthy children 9-16 years of age. Subjects were enrolled without consideration of prior dengue infection.*

6.1.4 Study Treatments or Agents Mandated by the Protocol

Composition:
Dengvaxia vaccine: Live, attenuated, tetravalent dengue virus vaccine
Form: Powder and solvent for suspension for injection.

Each 0.5 mL dose of reconstituted vaccine contains 4.5 to 4.9 log_{10} cell-culture infectious dose 50% ($CCID_{50}$) of each live, attenuated, recombinant, dengue serotype 1, 2, 3, 4 viruses
Excipients: essential amino acids, non-essential amino acids, L-arginine chlorhydrate, saccharose, D-trehalose dihydrate, D-sorbitol, tris (hydroxymethyl) aminomethane, and urea
Diluent: NaCl 0.4%
Batch number: Dengvaxia: S4317 and S4395. Solvent: D1118

Placebo: NaCl 0.9%.

6.1.5 Directions for Use

Dengvaxia vaccine: Dengvaxia vaccine is stored between +2°C and +8°C. The vaccine is used promptly after reconstitution and administered subcutaneously (SC) in the deltoid region.

Placebo: Solution stored between +2°C and +8°C. A 0.5 mL dose was withdrawn from the vial, and administered SC, promptly after preparation, in the deltoid region.

6.1.6 Sites and Centers

This study was conducted at multiple sites in four South and Central American countries and Puerto Rico as shown in Table 4 below.

Approximately half of all subjects were enrolled from study sites in Colombia. Participants from Puerto Rico accounted for 6% of the overall study population.

Table 4: Study CYD15, Country Distribution and Randomized Treatment Group in the Overall Population and in the Immunogenicity and Reactogenicity Subset- Randomized Subjects

Country	Dengvaxia Group (N=13,920) n (%)	Dengvaxia Immunogenicity/ Reactogenicity Subset n	Placebo Group (N=6,949) n (%)	Placebo Immunogenicity/ Reactogenicity Subset n	Total (N=20,869) n (%)	Total Immunogenicity/ Reactogenicity Subset n
All	13,920 (100)	1,334	6,949 (100)	666	20,869 (100)	2,000
Brazil	2,370 (17)	202	1,178 (17)	98	3,548 (17)	300
Colombia	6,497(46)	613	3,246 (47)	308	9,743 (46.6)	921
Honduras	1,866 (12)	200	933 (13)	100	2,799 (13.4)	300
Mexico	2,312 (17)	219	1,529 (17)	108	3,464 (16.6)	327
Puerto Rico	875 (6)	100	440 (6)	52	1,315 (6.3)	152

n: number of subjects randomized per country
N: number of subjects in Dengvaxia or Placebo groups
Subset: number of subjects in the immunogenicity and reactogenicity subset
Source: Adapted from STN 125682.0; Clinical Study Report CYD15, Version 4, Table 4.1

Clinical Reviewer Comment: *The applicant's rationale for planned enrollment of subjects per country was influenced by epidemiological data that supported higher rates of dengue transmission in Colombia at the time of the study and the objective of accruing enough dengue cases in the study. The applicant's rationale was acceptable; however, as expected, the*

proportion of subjects determined to be seropositive for prior dengue infection at baseline (pre-vaccination #1; see Table 17) and the dengue serotypes of infections during the study (see Figure 5) varied by country. This study was not powered to assess vaccine efficacy by country. Subjects were enrolled predominantly from sites in Colombia, and least from sites in Puerto Rico. Please see Section 7.0 (Integrated Overview of Efficacy) for additional discussion.

6.1.7 Surveillance/Monitoring

The surveillance/monitoring varied by phase of the clinical trial:

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 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. Passive surveillance was also conducted in which parents were instructed to contact the study team for episodes of febrile illness.

Hospital Phase (HP): The HP intended to assess vaccine safety related to hospitalization for VCD started at the end of the Active Phase (Month 25) and was continued for 3 years for all subjects. 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 SEP which reinitiated the active surveillance procedures performed during of the Active Phase. Those who did not consent continued with HP surveillance procedures up to 60 months post-dose #3.

Surveillance Expansion Phase (SEP): Upon reconsenting to participate in the SEP, 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 monitoring was conducted under the supervision of each individual site investigator.

There were Independent Data Safety Monitoring Committees (IDSMC's) for each site. Throughout the trial, the IDMC routinely reviewed SAEs and all dengue cases (including severe dengue) for signal detection purposes. The IDMC remained blinded as to which groups received vaccine.

Efficacy Evaluation
Case definition: Symptomatic VCD was defined as an acute febrile illness (i.e., temperature ≥ 38°C on at least 2 consecutive days) confirmed by dengue RT-PCR and/or dengue NS1 ELISA Ag test. Ascertainment for symptomatic, VCD cases began 28 days post dose #3 for a period of 12 months.

Safety Evaluation
SAEs (all subjects): During the Active Phase all SAEs were evaluated and during the HP only related SAEs, fatal SAEs and hospitalized VCD cases (which were considered a SAE) were evaluated. Hospitalized VCD cases and severe (clinically-severe or as per 1997 WHO criteria) VCD cases throughout the trial (from D0 until the end of the trial) (all subjects) were evaluated.

AESIs (all subjects): during the entire study, from M0 to M60. Serious AESIs were defined as serious, hypersensitivity/allergic reactions occurring in all subjects within 7 days after vaccination; neurotropic and/or viscerotropic AEs in all subjects within 30 days after vaccination. Specific guidelines were provided to the Investigator to help in the assessment of AEs that may be indicative of viscerotropic or neurotropic disease.

Solicited local (7 days) and systemic adverse reactions (14 days) occurring after each injection were recorded on diary cards and weekly phone calls; and during the active phase after the first 14 days by weekly phone calls in the Reactogenicity Subset (subset=2000 subjects).

Unsolicited non-serious AEs were monitored in the reactogenicity subset from Day 0 to D 28 by recording such events on daily diary cards.

Definition of dengue hemorrhagic fever (DHF):
The definition of DHF grade I, II, III, and IV were 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 X 10^9 /L)
- Plasma leakage as shown by hemoconcentration (hematocrit increased by 20% or more) or pleural effusion (seen on chest X-ray [CXR]) and/or ascites and/or hypoalbuminemia

The first two clinical criteria, plus thrombocytopenia and signs of plasma leakage were sufficient to establish a clinical diagnosis of DHF. Pleural effusion (seen on chest X-ray) and/or hypoalbuminemia provided supporting evidence of plasma leakage.

DHF was graded as follows:

Grade I: Fever accompanied by non-specific constitutional symptoms; the only hemorrhagic manifestation is a positive tourniquet test.

Grade II: Spontaneous bleeding in addition to the manifestations of Grade I patients, usually in the form of skin and/or other hemorrhages.

Grade III: Circulatory failure manifested by rapid and weak pulse, narrowing of pulse pressure (20 mmHg or less) or hypotension, with the presence of cold clammy skin and restlessness

Grade IV: Profound shock with undetectable blood pressure and pulse

Definition of clinically-severe dengue cases:
The Investigator considered the following potential manifestations of severity in all VCD cases; all dengue cases were reviewed by the IDMC who ensured consistent application of the term severe:

- 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.
- Myocarditis, pericarditis or heart failure (clinical heart failure) supported by chest X-ray (CXR), echocardiography, electrocardiogram (ECG) or cardiac enzymes where these are available

Tables 5 and 6 show the terminology, definitions and intensity scales for solicited injection reactions and solicited systemic adverse reactions that were used in trial CYD 15.

Table 5: Study CYD 15, Solicited Injection Site Reactions, Terminology, Definitions and Intensity Scale

MedDRA term	**Injection site pain**	**Injection site erythema**	**Injection site swelling**
Diary card term	Pain	Redness	Swelling
Definition		Presence of a redness including the approximate point of needle entry	Swelling at or near the injection site Swelling or edema is caused by a fluid infiltration in tissue or cavity and, depending on the space available for the fluid to disperse, swelling may be either soft (typically) or firm (less typical) to touch and thus can be best described by looking at the size of the swelling
Intensity scale	Grade 1: Easily tolerated Grade 2: Sufficiently discomforting to interfere with normal behavior or activities Grade 3: Incapacitating, unable to perform	Grade 1: > 0 to < 25 mm Grade 2: ≥ 25 to < 50 mm Grade 3: ≥ 50 mm	Grade 1: > 0 to < 25 mm Grade 2: ≥ 25 to < 50 mm Grade 3: ≥ 50 mm

Source: STN 125682.0; Clinical Study Report, CYD 15, version 4, Table 3.3

6: Study CYD 15, Solicited Systemic Adverse Reactions, Terminology, Definitions and Intensity Scale

MedDRA term	**Fever**	**Headache**	**Malaise**	**Myalgia**	**Asthenia**
Diary card term	Temperature	Headache	Feeling unwell	Muscle aches and pains	Weakness
Definition	Elevation of temperature to ≥ 38.0°C	Pain or discomfort in the head or scalp. Does not include migraine.	General ill feeling. Malaise is a generalized feeling of discomfort, illness, or lack of well-being that can be associated with a disease state. It can be accompanied by a sensation of exhaustion or inadequate energy to accomplish usual activities.	Muscle aches and pains are common and can involve more than one muscle at the same time. Muscle pain can also involve the soft tissues that surround muscles. These structures, which are often referred to as connective tissues, include igaments, tendons, and fascia (thick bands of tendons). Does not apply to muscle pain at the injection site which should be reported as njection site pain.	Generalized weakness.
Intensity scale[1]	Grade 1: ≥ 38.0°C to ≤ 38.4°C Grade 2: ≥ 38.5°C to ≤ 38.9°C Grade 3: ≥ 39.0°C	Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	Grade 1: No interference with activity Grade 2: Some interference with activity Grade 3: Significant; prevents daily activity	Grade 1: No nterference with activity. Grade 2: Some nterference with activity. Grade 3: Significant; prevents daily activity.

[1]For all reactions but fever, subjects or parents/guardians recorded the intensity level (Grade 1, 2, or 3) in the diary card. For fever, they recorded the body temperature, and the classification as Grade 1, 2, or 3 was assigned by the statistician.
Source: STN 125682.0; Clinical Study Report, CYD 15, version 4, Table 3.

Blood sampling: All subjects in the immunogenicity subset (n= total 2000): blood draws at baseline and 28 days post-dose 2 and 3 and annually for five years.

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

Table 7 shows the Table of study procedures for this CYD15 trial.

Table 7: Study CYD15, Table of Study Procedures

Visit Number	V01	V02	V03	V04	V05	V06	FUP 6M	V07	V08	V09	Vse+	V10	V11	V12
Trial Timelines	D0	D28	D180	V03 + 28 days	D365	V05 + 28 days	Last Vacc. + 6 months	Last Vacc. + 13 months	End of Active Phase	Last Vacc. + 24 months		Last Vacc. + 36 months	Last Vacc. + 48 months	Last Vacc. + 60 months
Time Windows (days)		+ 14	± 20	+ 14	± 20	+ 14	+ 30	± 30	± 30	± 30		± 30	± 30	± 30
Informed Consent/ Assent Form	X													
Inclusion/Exclusion Criteria	X													
Urine Pregnancy Test	X		X		X									
Contraindications	X		X		X									
Physical Examination	X													
Clinical Examination and Temperature	X		X		X									
History of YF Vaccination or Infection or Dengue Infection											X			
History of YF Vaccination or Infection or Dengue Infection/Vaccination	X									X		X	X	X
Concomitant Therapy			X		X									
Demography/Body Stature	X										X			
Randomization / IVRS/IWRS Contact	X		X		X									

Visit Number	V01	V02	V03	V04	V05	V06	FUP 6M	V07	V08	V09	Vse+	V10	V11	V12
Vaccination	Dose 1		Dose 2		Dose 3									
30-Min. Observation Period	X		X		X									
Memory Aid Provided/ Checked	X		X		X	X	X	X		X	X	X	X	X
Clinical Examination and Temperature	X		X		X									
Concomitant Therapy	X		X		X									
Injection Site Reactions and Systemic Events Assessment	X	X	X	X	X									
Diary Card Provided/Checked and Collected	X	X	X	X	X									
Blood (YF status)	X													
Blood (Dengue Neutralizing Abs)	X		X			X	X	X**++**	X	X		X	X	X
Blood (anti-Zika antibody response)						X		X				X	X	X

+Vse: Surveillance Expansion Period Visit for new addendum to the ICF and AF (or new ICF/AF as per local regulations), blood sample in subjects from the immunogenicity and reactogenicity subsets and in subjects with virologically-confirmed dengue thereafter (until the end of the trial).
++Blood draw on all subjects, 28 days post-dose 3
Blood (YF status): Neutralizing antibodies for YF virus measured at V0
Blood (Dengue Neutralizing Antibodies): measured by the $PRNT_{50}$ assay
Blood (anti-Zika response): measured by a (b) (4) assay
Source: Adapted from STN 125682.0; CYD 15 Study Protocol, version 8, "Table of Study Procedures", pp. 22-24

Clinical Reviewer Comment: *The efficacy evaluation was conducted according to WHO recommendations for a clinical definition of a dengue case to include a fever level and a requirement for laboratory confirmation of any dengue serotype infection. Safety assessment for local and systemic adverse reactions was assessed in a subset of subjects to characterize vaccine reactogenicity. The immunogenicity evaluation included only 10% of all subjects, therefore limiting the size of the study population for which analyses that were based upon dengue serostatus at baseline could be conducted. The SEP for assessment of any severe cases of dengue was necessary to assess any effect of Dengvaxia vaccine on the rates of severe dengue post-vaccination. Since severe dengue cases are almost always second or third, heterologous dengue cases, it was anticipated that this assessment would require several years of hospital follow up since severe dengue infections occur at rates that are much lower than any dengue infection.*

6.1.8 Endpoints and Criteria for Study Success

Primary Endpoint: symptomatic, VCD cases occurring > 28 days after Dose 3 (during the Active Phase) and defined as: acute febrile illness (i.e., temperature ≥ 38°C on at least 2 consecutive days); virologically-confirmed by dengue RT-PCR and/or dengue NS1 ELISA Ag test.

Study Success Criteria: Success on the primary efficacy endpoint was defined as demonstrating that the LB of the 95%CI was >25%.

Any one of the three diagnostic assays described below could be used to confirm virological infection:

Dengue Screen RT-PCR: Assessment and quantitation of dengue viremia was determined by testing serum samples with a nucleic-acid based assay. RNA was extracted from the serum to discard potential Taq polymerase inhibitors or interfering factors, using a commercial kit. Then, a RT-PCR was carried out with primers from a gene sequence conserved among dengue viruses. Due to a virus standard included in each run, results were expressed as a concentration of log10 plaque forming unit (PFU)/ml.

Simplexa Dengue RT-PCR: Serotype identification of post-infectious dengue viremia was determined by testing serum samples with a nucleic-acid based assay. Briefly, RNA was extracted from the serum to discard potential polymerase inhibitors or interfering factors, using a commercial kit. Then the Simplexa dengue RT-PCR assay was carried out which incorporated serotype-specific primers from dengue sequences. The results were expressed qualitatively and reported for each dengue serotype as detected or not detected.

This assay was used on all DS RT-PCR positive or Dengue NS1 Ag ELISA positive samples for serotype identification. In addition, sequencing analysis may be attempted on isolates from the serotyped samples.

Dengue NS1 Ag ELISA: The NS1 ELISA was performed using a commercially available kit: (b) (4)

Clinical Reviewer Comment: *A substantial proportion of dengue infections are not clinically apparent (up to 60% by W.H.O. estimates, reference 3) and will not be detected by this endpoint*

definition which requires at least two consecutive days of fever, T≥ 38°C. The requirement for an acute febrile illness with virological confirmation by dengue RT-PCR and/or NS1 ELISA Ag test was appropriate because the proposed indication is for the prevention of dengue disease, not dengue infection. The CBER CMC review team concurred that the diagnostic laboratory tests were adequately validated for its intended use (Please refer to the CBER CMC review memos). The success criteria for the primary efficacy endpoint was considered by CBER to be appropriate because the pre-specified LB of the 95%CI was well above 0.

Secondary endpoints:
Immunogenicity: Neutralizing Ab level against each of the four dengue virus strains of Dengvaxia constructs measured at baseline, after Dose 2, after Dose 3, and 1, 2, 3, 4 and 5 years after Dose 3 (PRNT50, dengue neutralization assay), and as from samples collected during the SEP; baseline neutralizing Ab response against Yellow Fever (YF) (YF neutralization assay). 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 seropositive subjects were those with titers ≥ 10 (1/dilution) against at least one dengue serotype at baseline

Safety: Occurrence of SAEs, including serious AESIs, collected in all subjects throughout the entire study. Occurrence of hospitalized virologically- confirmed dengue cases and occurrence of severe (clinically-severe or as per the 1997 WHO criteria) confirmed dengue cases, occurring during the SEP and during the trial.

Reactogenicity: Local and systemic adverse reactions were observed in a reactogenicity/immunogenicity subset of 10% of all randomized subjects.

Post-Hoc Analyses: Post-hoc analyses were conducted to clarify the relationship between dengue serostatus at baseline (pre-vaccination) and efficacy and risk of severe dengue post-vaccination as a function of dengue serostatus at baseline. Exploratory, post-hoc analyses were also conducted to clarify the imputed baseline dengue serostatus for subjects who were not in the immunogenicity subset. Analyses of vaccine efficacy by country were post-hoc analyses. Each such analyses are identified in the review as “exploratory post-hoc” analysis or “post-hoc” analysis in the Tables that present such data and in the narrative description of such findings.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Sample Size: A total of 20,875 subjects were to be enrolled: 13,917 subjects were to be included in the Dengvaxia Group and 6958 subjects in the Control Group. Assuming an alpha=2.5% (one-sided test), a yearly incidence of symptomatic VCD cases of 0.64%, an overall drop-out from the PPSE set of 20%, and a true VE of 70% after Dose 3, a total of 57 dengue cases were expected to provide > 90% power and obtain an LB of the 95% CI > 25% to show significant efficacy using the exact method. Under these assumptions, 57 PPSE dengue cases had to be collected to reach the 90% planned power.

Primary Objective:
The following hypotheses were tested using an alpha=2.5%: H0: VE ≤ 25%; H1: VE > 25%. The VE of Dengvaxia was considered significant if the LB of the 95% CI for the VE estimate was > 25%. The VE estimates in preventing symptomatic VCD cases were presented with their 95% CIs which were calculated using the exact method described by Breslow & Day. Based on the assumption that the true VE of Dengvaxia was 70% after 3 doses, a lost to follow-up rate of

10% over 2 years, a total of 57 dengue cases were expected to provide > 90% power and obtain a LB of the 95% CI of > 25% to show significant efficacy using the exact method.

Vaccine efficacy was evaluated on VCD cases, according to each dengue serotype after at least 1, 2 and 3 doses. VE is defined as 1 minus the ratio of density incidences of each serotype in the Dengvaxia Group over the density incidence of the Control Group.

The primary analysis was based on the Per Protocol Analysis Set (PPAS). Additional efficacy analyses were performed using the modified full analysis set for efficacy (mFASE). See Section 6.1.10.1 for definitions of populations analyzed.

Reactogenicity:
A subset of 2,000 subjects (1,333 in the Dengvaxia Group and 667 in the Control Group) was included in the reactogenicity analysis that described both solicited and unsolicited events. 1,333 subjects in the Dengvaxia Group gave a probability of 95% of observing an event with a true incidence of 0.23% (rule of three).

Analyses
Safety:
Hospitalized and severe VCD cases were described throughout the SEP and throughout the trial in each treatment group, overall and yearly. Incidence, RR and their 95% CIs were computed based on the same methodology as for primary endpoint, as RR was derived from VE as RR= (1- (VE/100)).

The number of SAEs throughout the trial was analyzed in each group and by time:

- Within 28 days post-dose 1 period
- Beyond 28 days post-dose 1 period and between 28 days after the last injection until 6 months)
- Within 6-month follow-up period (i.e., all SAE occurred up to 6 months after the last injection)

Immunogenicity:
In a subset of 2,000 subjects (1,333 in the Dengvaxia Group and 667 in the Control Group):

- GMT for each serotype (parental strains) before the first injection and 28 days after the second and the third injections, and 1, 2 and 3 years after the third injection;
- Geometric mean of the individual titer ratios (GMTR) for each serotype (parental strains) 28 days after the second and the third injection, and 1, 2, and 3 years after the third injection, based on the baseline neutralizing Ab titer;
- Number and percentage of subjects with dengue neutralizing Ab titer ≥ 10 (1/dil) (parental strains) 28 days after the second and the third injections, and 1, 2, and 3 years after the third injection;
- Number and percentage of subjects with dengue neutralizing Ab titer ≥ 10 (1/dil) against at least one, two, three, or the four dengue serotypes.
- Distribution of GMTs was described at each available time point.
- The 95% CIs were calculated using: The normal approximate method for GMTs and GMTRs; The exact binomial distribution for percentages (Clopper-Pearson's method).
- Please refer to the statistics review for details concerning the statistical analysis plan.

Clinical Reviewer Comment: *The statistical analysis plan (SAP) was appropriate for clinical endpoint efficacy studies. There were no significant changes in the SAP after the study was initiated. Please see CBER Biostatistics Review for further details.*

6.1.10 Study Population and Disposition

Per Protocol Analysis Sets (PPAS): all subjects who had no protocol deviations. There were two per protocol analysis sets: PPSE was for efficacy and PPSI was for immunogenicity. The primary efficacy analysis was performed on the PPSE and was confirmed on the mFASE. In the mFASE, subjects were analyzed according to the group, as randomized. Subjects were excluded from the per-protocol analysis set for efficacy (PPSE) for the following reasons:

- Subject did not meet at least one of the protocol-specified inclusion/exclusion criteria and did not respect the definite contraindications
- Subject did not receive the correct number of injections
- Subject received at least one dose of a product other than the one that he/she was randomized to receive
- Administration of vaccine was not done as per-protocol (site and route of administration)
- Subject did not receive vaccine in the time window defined in the Table of study procedures
- Subject received a protocol-restricted therapy or vaccine from Category 2
- Subject with an emergency un-blinding performed by the Investigator
- Subject did not have at least one contact point after 28 days post-injection 3 and before the end of the active surveillance period
- Subject had serious non-compliance to GCP
- Subject had serious non-compliance to surveillance system
- Subjects were to remain in this population until they met one of the above criteria (except for the 2 last criteria). The PPSE set was used for the analysis of VE from 28 days post-dose 3 to the end of the Active Phase.

Full Analysis Set for Efficacy (FASE): all subjects who received at least one injection and who did not have serious non-compliance to GCP.

modified Full Analysis Set for Efficacy (mFASE): all subjects who received 3 injections, regardless of the per-protocol criteria and who did not have serious non-compliance to GCP.

Full Analysis Set for Surveillance Expansion (FASSEP): all subjects who received at least one injection and who accepted to be included in the Surveillance Expansion period.

Full Analysis Set for Immunogenicity (FASI): subjects of the immunogenicity subset 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 good clinical practice (GCP).

Full Analysis Set for Antibody Persistence (FASAb): subjects of the immunogenicity subset who received at least one injection.

Safety Analysis Set (SAS): The safety analysis set is defined for each dose as the subset of subjects who received this dose and who did not have serious non-compliance to GCP. Subjects were analyzed according to the treatment received. For the analysis at any dose, subjects were analyzed according to the treatment received at the first dose.

Clinical Reviewer Comment: *The analysis sets were appropriate to the assessment of efficacy, safety and immunogenicity.*

6.1.10.1.1 Demographics
Table 8 shows the distribution by gender, age, and age group for trial CYD15.

Table 8: Study CYD15, Baseline Demographic by Treatment Group - Safety Analysis Set

Demographic	Dengvaxia Group (N=13,915)	Placebo Group (N=6,939)	All (N=20,854)
Male, n (%)	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)
Sex ratio: Male/Female	0.98	0.97	0.97
Age (years):	--	--	--
Mean (SD)	12.5 (2.14)	12.5 (2.13)	12.5 (2.14)
Min; Max	9.0; 17.0	9.0; 17.0	9.0; 17.0
Median	12.3	12.3	12.3
Q1; Q3	10.7; 14.2	10.7; 14.2	10.7; 14.2
Age group:	--	--	--
9 to 11 years, n (%)	6,305 (45.3)	3,146 (45.3)	9,451 (45.3)
12 to 16 years, n (%)	7,610 (54.7)	3,793 (54.7)	11,403 (54.7)

n: number of subjects fulfilling the item listed
Source: STN125682.0; Clinical Study Report CYD 15, version 4, Table 10.22

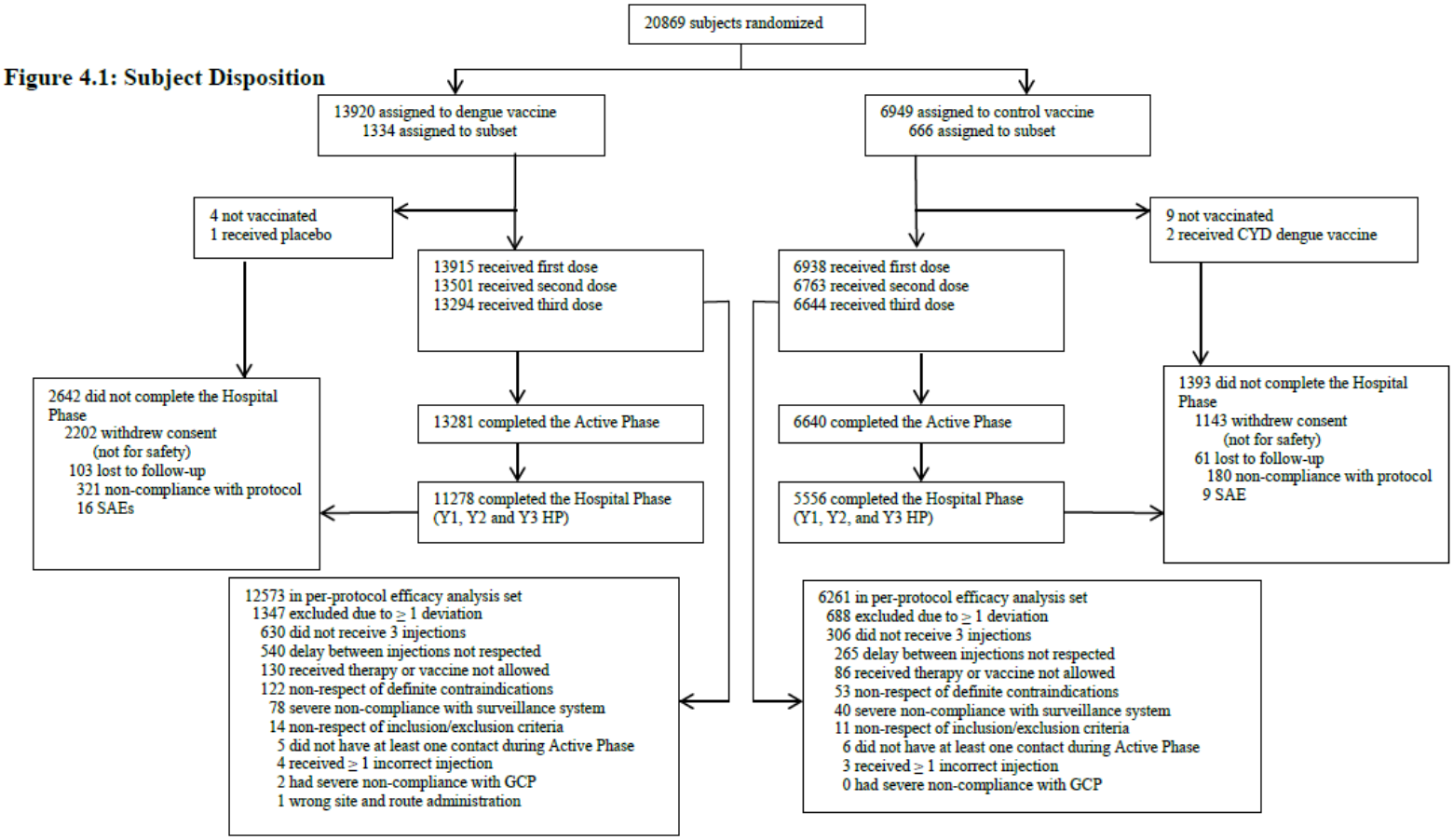
Clinical Reviewer Comment: *Sex, age and age sub-groups were equally balanced between Dengvaxia and Placebo groups. Race and ethnicity identification were assessed and 100% of all subjects identified as "Hispanic" by ethnicity; 8% identified as white, non-hispanic; 3% as black and 16% as American Indian. There are indigenous groups in most South American countries who identify as "Indian" and there are people who identify as "black" and there are people who identify as "white" although this is a minority of the population. One of the main reasons to request racial or ethnic identification in a vaccine study is to have the ability to differentiate vaccine effects that may be genetically [racially] influenced. There were no exploratory analyses conducted for this study by either racial or ethnic characterization.*

6.1.10.1.2 Medical/Behavioral Characterization of the Enrolled Population
No identifiable medical or behavioral characteristics for the study population were collected.

Clinical Reviewer Comment: *A behavioral characteristic that could have impacted the study results would have been any personal protection measures or vector control strategies that would have impacted the likelihood of exposure to potentially infectious mosquito bites; however, such measures are not systematically employed in dengue endemic regions and any incidental measures were assumed to be evenly distributed at these clinical study*

6.1.10.1.3 Subject Disposition
Figure 2, below, shows the subject disposition for study CYD15.

. **Figure 2: Subject Disposition for Study CYD 15.**



Reviewer Comment: *Subject disposition was very similar between the vaccine and placebo control groups, with a very high rate (>95%) of compliance with study procedures during the 12-month vaccination time and subsequent 12-month active case detection time. This high compliance rate gives confidence that this study reflects actual differences between vaccine and control groups on outcome parameters such as immune responses and vaccine efficacy observed in the active phase. During Year 5 of the study (i.e. 48 months after the third vaccination), the proportion of subjects who participated in Year 3 of HP and re-consented to participate in the SEP was balanced between active treatment and placebo control groups, thus giving confidence that any imbalances in reported severe/hospitalized dengue cases during this time period was not likely due to an imbalance among the two study groups with regard to subjects prematurely withdrawing from the study or surveillance methods.*

Compliance with protocol procedures was very high in both groups during the 12-month period vaccination period. Of a total of 20,869 randomized subjects, >99% of all subjects received the first dose, 97% received the second dose and 95% received the third dose in each group. In each group, 95% of subjects completed the active phase [defined as the 12 months required for the three-dose series and the 12-month period commencing 28 days post dose 3 for active case detection of any virologically confirmed dengue case].

After implementation of protocol amendment #4, participants were notified of the need to consent / decline to enter the SEP, which occurred during Year 5 of the study (i.e., up to 48 months after the third injection, initially designated Year 3 of HP). 1858 [13.3%] and 970 [14.0%] subjects in the Dengvaxia Vaccine group and Control group, respectively, did not re-consent to participate in the SEP; these participants were classified as voluntarily withdrawing from Year 3 of HP. Thus, 11,278 [81.0%] in the Dengvaxia Group and 5556 [80.0%] in the Control Group completed Visit 11 (end of Year 5 of the study, now termed Year 3 of HP/SEP). The SEP was ongoing at the time the interim report for this study was prepared.

6.1.11 Efficacy Analyses

The primary objective was to assess the efficacy of dengvaxia after 3 injections (at 0, 6 and 12 months) in preventing symptomatic VCD cases, regardless of severity, due to any of the four serotypes.

6.1.11.1 Analyses of Primary Endpoint(s)

The primary endpoint was symptomatic VCD cases occurring > 28 days after Dose 3 until the end of the Active Phase (i.e., up to 13 months after the third vaccination). Symptomatic VCD was defined as: acute febrile illness (i.e., temperature ≥ 38°C on at least 2 consecutive days) and confirmed by dengue RT-PCR and/or dengue NS1 ELISA Ag test.

Table 9 shows the primary efficacy results based on the PPSE. The primary objective was met, since the lower bound of 95% CI for the VE was > 25%.

Table 9: Study CYD15, Vaccine Efficacy Against Symptomatic, VCD[a] Post Dose #3, Due to Any of the Four Dengue Serotypes: Per Protocol Analysis Set for Efficacy

Treatment group	Dengvaxia Group (N[b]=12,574)	Placebo Group (N=6,261)	VE (95%CI)
Symptomatic, VCD Cases[c]	176	221	**60.8%** (52.0;68.0)[d]

[a] VCD: Virologically-confirmed dengue
[b]N:number of subjects in Dengvaxia or Placebo groups
[c]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.
[d]Vaccine efficacy was considered statistically significant if the lower bound of its 95% CI was >25%.
Source: Adapted from STN 125682.0; CYD15 Interim Clinical Study Report, Version 4, Table 5.1.

Clinical Reviewer Comment: *Trial CYD15 is one of the two Phase 3 trials with a clinical efficacy endpoint of VCD disease due to any of the four dengue serotypes. The observed VE of 60.8% (52.0;68.0) met the pre-specified success criteria of an LB of 95%CI of >25%. This analysis includes children who were seronegative and seropositive pre-vaccination. Please see Table 18 for an analysis of efficacy of Dengvaxia by baseline immune status.*

6.1.11.2 Analyses of Secondary Endpoints

Efficacy
VE against DHF of any grade (Table 10) and against clinically severe dengue (Table 11) were evaluated as secondary descriptive endpoints. Please refer to Section 6.1.7, Safety Evaluation, for definition and classification of DHF by WHO criteria. Clinically severe dengue was assessed by the IDMC and used the same clinical criteria, according to an algorithm, as was used to define DHF.

Table 10: Study CYD 15, Vaccine Efficacy Against Virologically-Confirmed Dengue Cases Meeting DHF WHO Criteria During the Active Phase Due to Any and Each Dengue Serotype - Full Analysis Set for Efficacy[1]

DHF Grade and Serotype criteria	Grade	CYD* cases	Placebo cases	VE %	95% CI
Virologically-Confirmed cases meeting DHF WHO criteria due to any of the 4 serotypes	**Any grade**	1	10	**95.0**	(64.9; 99.9)
--	**Grade I**	0	2	**100.0**	(-165.8; 100.0)
--	**Grade II**	1	8	**93.8**	(53.5; 99.9)
--	**Grade III**	0	0	NC	(NC)
--	**Grade IV**	0	0	NC	(NC)
Serotype 1	**Any grade**	1	3	**83.4**	(-106.4; 99.7)
Serotype 2	**Any grade**	0	3	**100.0**	(-20.5; 100.0)
Serotype 3	**Any grade**	0	3	**100.0**	(-20.4; 100.0)
Serotype 4	**Any grade**	0	1	**100.0**	(-1,837.1; 100.0)
Unserotyped	**Any grade**	0	0	NC	(NC)

[1]Full Analysis Set for Efficacy: all subjects who had at least one injection
NC: Not Computable
*CYD Cases: (CYD is Dengvaxia); number of subjects who received either CYD (Dengvaxia) or Placebo with at least one virologically-confirmed dengue episode meeting the pre-specified DHF WHO criteria from D0 to the end of Active Phase.
Source: Adapted from STN 125682.0; Clinical Study Report, CYD 15, Table 5.10

Clinical Reviewer Comment: *Vaccine efficacy against DHF of any grade was assessed, however there were limited numbers of cases of DHF in this study and there were only DHF grades 1 and 2 observed. DHF was observed at a higher rate in the placebo as compared to the Dengvaxia group. CYD 15 was not powered to assess efficacy against DHF and this effect should be viewed as observational and it is not supportive of an indication for prevention of DHF*

Table 11. Study CYD 15, Vaccine Efficacy Against Clinically Severe Virologically-Confirmed Dengue Cases During the Active Phase Due to Any and Each Serotype – Full Analysis Set for Efficacy[1]

Severe (according to IDMC assessment) virologically-confirmed cases	Dengvaxia Group Cases (N=13,914)	Placebo Group Cases (N=6,940)	VE % (95%CI)
Due to any of the 4 serotypes	1	11	**95.5** (68.8; 99.9)
Serotype 1	1	3	**83.4** (-106.4; 99.7)
Serotype 2	0	4	**100.0** (24.6; 100.0)
Serotype 3	0	3	**100.0** (-20.4; 100.0)
Serotype 4	0	1	**100.0** (-1,837.1; 100.0)
Unserotyped	0	0	NC

[1]Full Analysis Set for Efficacy: all subjects who had at least one injection
NC: not calculable
Cases: number of subjects with at least one clinically (assessed by IDMC) severe virologically-confirmed dengue episode from D0 to the end of Active Phase, which was M25.
Source: Adapted from STN 125682.0; Clinical Study Report, CYD 15, Table 5.12

Clinical Reviewer Comment: *The assessment of clinically severe, VCD cases was based on similar criteria as that used for the assessment of DHF and the results are similar, with more cases of clinically severe cases in the placebo group than the Dengvaxia group. There were 11 cases of DHF of any grade (Table 10) and 12 cases of clinically severe dengue (Table 11). All 11 cases of DHF were also classified as clinically severe cases and one case of clinically severe dengue was not classified as DHF. CYD 15 was not powered to assess efficacy against clinically severe dengue and this effect should be viewed as observational and it is not supportive of an indication for prevention of clinically severe dengue.*

Clinically severe dengue during the entire study from M0 to M60: Severe, VCD cases were assessed as a SAE and were monitored during the entire trial period from M0 to M60. In response to an Information Request, (STN125682.28, on 3-4-2019) applicant provided a tabular listing of each subject in CYD15 who had an assessment of severe clinical dengue during this full study period (data in Tables 10 and 11 are from the Active Phase, M0 to M25). 26 cases of severe dengue were observed, 16 in the Placebo Group and 10 in the Dengvaxia Group. Fifteen cases of severe dengue were serotype 1; 8 were serotype 2; 2 were serotype 3 and 1 was serotype 4. These 26 cases include the 12 cases shown in Table 11 plus an additional 14 cases that were observed between M26 and M60.

Clinical reviewer comment: *In the opinion of this reviewer, these data on DHF and clinically severe dengue are observational and do not support an indication to prevent DHF or severe clinical dengue. However, the level of protection against clinically severe dengue is not as high for the entire trial period of 60 months as it is during the first 25 months of the Active Phase.*

VE by serotype is shown in Table 12. Study CYD15 was not powered to assess serotype-specific efficacy and there were no success criteria for this endpoint.

Table 12: Study CYD15, Vaccine Efficacy Against Symptomatic Virologically-Confirmed Dengue Post-dose 3, Due to Any and Each Serotype - modified Full Analysis Set for Efficacy[1]

Treatment Group	Dengvaxia Group (N=13,288) Cases[a]	Placebo Group (N=6,643) Cases[a]	VE % (95% CI)
Due to any of the 4 serotypes	185	236	**61.3** (52.8; 68.2)
Serotype 1	66	66	**50.3** (29.1; 65.2)
Serotype 2	58	50	**42.3** (14.0; 61.1)
Serotype 3	43	82	**74.0** (61.9; 82.4)
Serotype 4	18	40	**77.7** (60.2; 88.0)
Unserotyped	6	3	**0.0** (-517.8; 78.6)

[1]ModifiedM Full Analysis Set for Efficacy: all subjects who received three doses, analysis done post-dose 3
[a]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.
Subjects with a virologically-confirmed dengue of the studied serotype between V01 and 28 days after injection 3 are excluded from the corresponding serotype-specific analysis.
Source: Adapted from STN 125682.0; CYD 15 Interim Clinical Study Report, Version 4, Table 5.2

Reviewer Comment: *The study was not powered to evaluate serotype-specific VE and there were no pre-specified success criteria for efficacy by serotype. VE by serotype varied, which is consistent with the results of the Phase 2 study, CYD23 (see Section 6.3). The point estimates for VE were higher for serotypes 3 and 4 (lower bound of the 95%CIs>60%) compared to serotypes 1 and 2 (wider CIs; lower bound of the 95%CI >14%). Although most dengue endemic countries have reported either all four serotypes in circulation or 3 of the 4 serotypes, there usually are one or two predominant serotypes in any given dengue transmission cycle.*

Immunogenicity
Dengue neutralizing antibody GMTs by serotype using the $PRNT_{50}$ assay are presented in Table 13. In the immunogenicity subset, neutralizing antibodies for each dengue vaccine serotype were measured at baseline (pre-vaccination #1), 28 days after Dose #2 and after Dose #3; and 1, 2, 3, 4 and 5 years after Dose #3. Dengue neutralizing antibody titers were measured at 28 days post-dose #3 for all subjects. 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 seropositive subjects were those with titers ≥ 10 (1/dilution) against at least one dengue serotype at baseline.

Table 13 shows dengue vaccine serotype GMTs for the immunogenicity subset, by study group, from pre-vaccination #1 to four years following Dose #3.

Table 13: Study CYD15, GMTs of Dengue Antibodies at Pre and Post Vaccination Timepoints Against Each Serotype with the Parental Dengue Virus Strains– Full Analysis Set for Immunogenicity

Treatment Group	Dengvaxia Group (N=1,301, M=1,069-1,300) GMT	Dengvaxia Group (95%CI)	Placebo Group (N=643, M=528-640) GMT	Placebo Group (95%CI)
Pre-Dose 1 Serotype 1	128	(112; 145)	119	(98.7; 142)
28 Days Post-Dose 3	395	(353; 441)	121	(101; 145)
1-Year Follow-Up Post-Dose 3	266	(234; 302)	146	(121; 176)
2-Year Follow-Up Post-Dose 3	209	(185; 237)	142	(118; 171)
3-Year Follow-Up Post-Dose 3	259	(229; 293)	177	(147; 214)
4-Year Follow-Up Post-Dose 3	397	(347; 455)	283	(227; 353)
Pre-Dose 1 Serotype 2	138	(123; 156)	115	(97.2; 136)
28 Days Post-Dose 3	574	(528; 624)	129	(109; 152)
1-Year Follow-Up Post-Dose 3	371	(336; 409)	145	(122; 173)
2-Year Follow-Up Post-Dose 3	339	(307; 374)	173	(146; 206)
3-Year Follow-Up Post-Dose 3	342	(311; 376)	187	(157; 222)
4-Year Follow-Up Post-Dose 3	387	(346; 432)	241	(199; 292)
Pre-Dose 1 Serotype 3	121	(108; 136)	114	(95.9; 136)
28 Days Post-Dose 3	508	(465; 555)	124	(105; 147)
1-Year Follow-Up Post-Dose 3	292	(263; 325)	137	(114; 165)
2-Year Follow-Up Post-Dose 3	303	(274; 334)	170	(142; 203)
3-Year Follow-Up Post-Dose 3	326	(295; 362)	186	(156; 223)
4-Year Follow-Up Post-Dose 3	371	(331; 416)	237	(193; 290)
Pre-Dose 1 Serotype 4	43.6	(39.6; 48.0)	39.0	(33.9; 44.7)
28 Days Post-Dose 3	241	(226; 258)	44.3	(38.6; 50.8)
1-Year Follow-Up Post-Dose 3	174	(161; 188)	51.5	(44.3; 59.8)
2-Year Follow-Up Post-Dose 3	138	(128; 149)	56.5	(48.8; 65.5)
3-Year Follow-Up Post-Dose 3	173	(160; 185)	76.5	(66.1; 88.6)
4-Year Follow-Up Post-Dose 3	190	(173; 208)	101	(85.1; 119)

N: number of subjects enrolled; M: number of subjects available for the endpoint.
Source: Adapted from STN 125682.0; Clinical Study Report, CYD 15, Table 6.3

Clinical Reviewer Comment: *For each of the four vaccine serotypes, the post-dose #3 GMTs in the Dengvaxia vaccine group were 3-6 times higher than the pre-dose titers. There was at least a 25% reduction in GMT's at 1-year post dose #3 compared to GMTs at 1-month post-vaccination #3, and no further reduction in titers at the subsequent 2, 3 and 4-year time points. At three years post-vaccination #3, GMTs in vaccinated subjects were higher than baseline, for all serotypes. In the control group, there was, as expected, no increase in GMTs following dose, although there was a general trend of increasing GMT titers over the four years follow up period. These data support the conclusion that Dengvaxia vaccine is immunogenic for each serotype.*

The overall trend to higher titers in both study groups through the year 4 follow up may be associated with natural exposure to and infection with dengue serotypes during that period. This analysis includes subjects who were dengue seropositive and dengue seronegative at baseline.

An exploratory, post-hoc analysis of Dengue GMTs (PRNT50 assay) was conducted by baseline dengue serostatus at baseline and is shown in Table 14. Subjects in the Dengvaxia group who were seropositive (titers $\geq$ 10 [1/dil]) for dengue at baseline had substantially higher GMTs following vaccination #3 than subjects who were seronegative (titers < 10 [1/dil]) for dengue at baseline.

Table 14: Study CYD15, GMTs of Dengue Antibodies Against Each Serotype with the Parental Dengue Virus Strains, by Dengue Status at Baseline– Full Analysis Set for Immunogenicity

Treatment group	Dengue Seropositive, Dengvaxia Group (M=1,040-1,048) GMT (95%CI)	Dengue Seropositive, Placebo Group (M=494-495) GMT (95%CI)	Dengue Seronegative, Dengvaxia Group (M=249-251) GMT (95%CI)	Dengue Seronegative, Placebo Group (M=143-145) GMT (95%CI)
Serotype 1 Pre-Dose 1	278 (247;313)	302 (265;355)	5.00 (NC)	5.00 (NC)
Serotype 1 Post-Dose 3	703 (634;781)	272 (230;321)	35.3 (30;42)	7.34 (6;9)
Serotype 2 Pre-Dose 1	306 (277;338)	291 (254;334)	5.00 (NC)	5.00 (NC)
Serotype 2 Post-Dose 3	860 (796;930)	297 (258;341)	105 (89;125)	7.23 (6;9)
Serotype 3 Pre-Dose 1	261 (235;289)	286 (247;332)	5.00 (NC)	5.00 (NC)
Serotype 3 Post-Dose 3	762 (699;830)	279 (240;324)	93.6 (80;109)	7.55 (6;9)
Serotype 4 Pre-Dose 1	73.3 (67;81)	71.5 (62;82)	5.00 (NC)	5.00 (NC)
Serotype 4 Post-Dose 3	306 (286;328)	77.2 (67;89)	89.5 (76;105)	6.55 (6;8)

M: number of subjects available for the endpoint; NC: not calculable
Neutralizing antibodies measured by a dengue PRNT assay.
Dengue seropositive subjects at baseline are defined as subjects with titers >= 10 (1/dil) against at least one dengue serotype at baseline. Dengue seronegative subjects at baseline are defined as subjects with titers < 10 (1/dil) against all four serotypes at baseline (undetectable titers imputed to 5).
Source: Adapted from 125682.0; CYD15 Interim Clinical Study Report, Version 4, Table 6.6.

Clinical Reviewer Comment: *For each vaccine serotype, the GMTs were substantially higher post-doses #1, #2, and #3, in subjects who were baseline dengue seropositive compared to*

subjects who were baseline dengue seronegative. In subjects who were dengue seronegative at baseline, the neutralizing antibody responses following Dengvaxia vaccination were minimal. This was an exploratory, post-hoc analysis of the immunogenicity subset which was comprised of 10% of all subjects.

Dengue GMTs (PRNT assay) by virologically-confirmed case and non-case during the Active Phase: this was an exploratory analysis. There was a tendency towards higher vaccine efficacy with increases in post-vaccination GMT, as shown in Table 15. There was no specific neutralizing antibody titer that represented a correlate of protection.

Table 15: Study CYD15, GMTs of Dengue Antibodies Against Each Serotype with the Parental Dengue Virus Strains for Dengue Cases and Non-Cases, Post-dose 3 - Dengue PRNT50 assay – modified Full Analysis Set for Efficacy

Dengue Virus Serotype	Dengvaxia Cases M	Dengvaxia Cases GMT (95% CI)	Dengvaxia Non-Cases M	Dengvaxia Non-Cases GMT (95% CI)	Placebo Cases M	Placebo Cases GMT (95% CI)	Placebo Non-Cases M	Placebo Non-Cases GMT (95% CI)
Serotype 1	65	50 (35;73)	1274	407 (364;454)	66	12 (9;17)	608	125 (104;150)
Serotype 2	58	70 (47;103)	1274	584 (537;635)	50	43 (25;72)	608	128 (108;152)
Serotype 3	43	239 (177;324)	1274	519 (475;567)	82	38 (27;53)	608	125 (105;149)
Serotype 4	18	78 (43;140)	1274	244 (228;262)	39	15 (11;22)	608	46 (40;52)

M: number of subjects with available data for the relevant endpoint.
Cases are subjects with at least one virologically-confirmed dengue case between 28 days post-dose 3 and the end of the Active Phase due to the considered serotype. Non-cases are subjects in the FASI who do not have virologically-confirmed dengue due to any serotype since V01 to the end of the Active Phase.
Source: Adapted from Original 125682; CYD15 Interim Clinical Study Report, Version 4, Table 6.7

Clinical Reviewer Comment: *The GMTs in cases and non-cases should be interpreted cautiously. There were cases of symptomatic, VCD in subjects who had neutralizing antibody titers like those observed, on average, in non-cases. Multiple linear regression analysis did not identify a specific neutralizing antibody titer predictive of protection. The applicant and CBER concluded that there was no correlate of protection identified by $PRNT_{50}$ GMT responses. The applicant assessed that there was a "trend" towards higher efficacy with higher GMTs, however CBER assesses that the term "tendency" better describes this relationship between higher GMTs and efficacy since tendency does not imply a specifically quantifiable relationship. It is likely that there is a role for both the quantity of antibody responses and the avidity of those responses in determining protection from dengue infection, as suggested by the finding that high serotype 2 post-vaccination GMTs occurred and yet the estimate for vaccine efficacy for serotype 2 is the lowest of all four serotypes. Additionally, there may be a role for cell-mediated immune responses (CMI) in the protection induced by Dengvaxia vaccination and such responses were not assessed in this trial.*

6.1.11.3 Subpopulation Analyses

Efficacy:
There was a mild difference in efficacy by sex, with females having 6-8% lower efficacy than males (Data not shown for this study. Please see Section 7 for sex-based efficacy differences.).

Efficacy varied slightly by age, with higher VE estimates in individuals 12-16 years of age; however, this difference was likely related to a higher percentage of subjects ages 9-16 years who were dengue seropositive at baseline, not by age *per se.* (Data not shown for this study. Please see Section 7 for age-related differences in efficacy by pooled analyses.)

Differences were observed in VE according to dengue serostatus at baseline, with higher efficacy in subjects who were dengue seropositive at baseline compared to those who were dengue seronegative. (Please see Section 6.1.11.5, Table 18. Please see Section 7 for differences in efficacy related to dengue serostatus at baseline, pre-vaccination, by pooled analysis of studies.).

Differences in serotype-specific efficacy by country were also noted, likely due to differences in dengue seroprevalence rates in individuals 9-16 years of age in each country. VE varied from 56% (Puerto Rico) to 92% (Colombia). (Please see Section 6.1.11.5, Table 17. Please see Section 7 for differences in efficacy by country for all studies reviewed.)

Clinical Reviewer Comment: *The major finding from subpopulation analyses was the differences in VE by dengue serostatus at baseline (pre-vaccination #1). Compared to subjects who were dengue seropositive, the vaccine induced substantially lower GMTs, and correspondingly lower VE, in subjects who were dengue seronegative at baseline. Please see Section 7 for these analyses based upon pooled data from all three efficacy trials.*

Immunogenicity:
There was no effect of sex on immunogenicity. There was a small effect on immunogenicity by age, with subjects 9-11 years of age having mildly reduced immune responses post-dose #3 compared to subjects 12-16 years of age.

6.1.11.4 Dropouts and/or Discontinuations

During the Active Phase, 10 subjects in the Dengvaxia Group (due to 7 SAEs and 3 AEs) and 9 in the Control Group (due to 9 SAEs) prematurely discontinued from the study. No serious or non-serious AEs that led to study termination occurred within 28 days after any dose.

A total of 19,933 (95.5%) randomized subjects (13,290 [95.5%] in the Dengvaxia Group and 6643 [95.6%] in the Control Group) completed the vaccination period. Reasons for discontinuation during the vaccination period were mostly voluntarily withdrawals not due to an AE (3.0% in the Dengvaxia Group and 3.1% in the Control Group), and noncompliance with study procedures (1.1% in the Dengvaxia Group and 0.9% in the Control Group), mostly due to pregnancy. Other reasons for discontinuation were “lost to follow up” (0.3% in each of the 2 groups), and “occurrence of a SAE” or occurrence of “Other AEs” (0.1% or less in the 2 groups).

Clinical Reviewer Comment: *There was a very small percentage of subjects in both groups who discontinued due to AE's (0.1% or less in each study group) and the rate of discontinuations was balanced between Dengvaxia and placebo control groups; therefore, these discontinuations would not be expected to have an influence on the overall safety assessment of this study.*

Protocol deviations in the study are displayed in Table 16.

Table 16: Study CYD15, Summary of Protocol Deviations Leading to the Exclusion of Subjects from the PPSE - Randomized Subjects

Treatment Group	Dengvaxia Group n (%)	Placebo Group n (%)	Total n (%)
Protocol Set for Efficacy	12,573 (90.3)	6,261 (90.1)	18,834 (90.2)
Subject with at least one deviation	1,347 (9.7)	6,88 (9.9)	2,035 (9.8)
Did not meet all protocol specified inclusion/exclusion criteria	14 (0.1)	11 (0.2)	25 (0.1)
Did not respect the definite contraindications	122 (0.9)	53 (0.8)	175 (0.8)
Did not receive the correct number of doses	630 (4.5)	306 (4.4)	936 (4.5)
Received at least one dose of a product other than the one assigned by randomization*	4 (0.0)	3 (0.0)	7 (0.0)
Did not receive vaccine in the time window defined in the Table of study procedures	540 (3.9)	265 (3.8)	805 (3.9)
Received a protocol-restricted therapy or vaccine from Category 2	130 (0.9)	86 (1.2)	216 (1.0)
Serious non-compliance with the surveillance system	78 (0.6)	40 (0.6)	118 (0.6)

n: all subjects in the per protocol set
Source: STN 125682.0; Clinical Study Report, version 4, Table 4.6

Clinical Reviewer Comment: *The percentage of subjects with protocol deviations were balanced between vaccine and control groups.*

6.1.11.5 Exploratory and Post Hoc Analyses

Dengue seropositive (seropositive) subjects at baseline are defined as subjects with titers >= 10 (1/dil) against at least one dengue serotype at baseline. Dengue seronegative subjects at baseline are defined as subjects with titers < 10 (1/dil) against all four serotypes at baseline.

Table 17. Study CYD15, Vaccine Efficacy and Percentage of Subjects Dengue Seropositive at Baseline, by Country, Post-Hoc Analysis

Country (Number of Sites)	Dengue Seropositive at Baseline (%)	VE: Any Serotype
Brazil (8)	74	79.4 (60.4;89.8)
Colombia (5)	93	66.0 (53.9;75.1)
Honduras (4)	88	69.5 (53.3;80.4)
Mexico (2)	57	8.8 (-50.3;43.5)
Puerto Rico (4)	56	43.4 (-68.5;80.6)

Source: STN 124682.0; Clinical Study Report for CYD 15, version 4, Table 4.12; ISE, Table 3.4.5.3

Clinical Reviewer Comment: *In post-hoc analyses, vaccine efficacy against symptomatic, VCD cases varied by country and by serotype-specific efficacy (data not shown) within countries. These analyses should be viewed descriptively and with caution as this study was not powered for these specific endpoints. The percentage of subjects who were dengue seropositive at baseline varied from 56% in Puerto Rico to 93% in Colombia and the dominant dengue serotypes circulating in each country varied during the Active Phase of the study. Dengue serostatus at baseline and predominant dengue serotypes in circulation are both likely to influence vaccine efficacy for any given year in various countries. Please see Section 7 for additional discussion of Dengvaxia VE by country.*

VE during the Active Phase, by dengue serostatus at baseline, is shown in Table 18.

Table 18. Study CYD15, Vaccine Efficacy Against Symptomatic Virologically-Confirmed Dengue Cases, During the Active Phase*, Due to Any of the 4 Dengue Serotypes, by Baseline Dengue serostatus- Full Analysis Set for Immunogenicity (FASI)

Study Group	Dengue Seropositive, Dengvaxia Group (n=1,073)	Dengue Seropositive, Placebo Group (n=512)	Dengue Seronegative, Dengvaxia Group (n=258)	Dengue Seronegative, Placebo Group (n=149)
Number of Cases, any serotype	8	23	9	9
Vaccine Efficacy % (95% CI)	**83.7** (62.2; 93.7)	--	**43.2** (-61.6; 80.0)	**--**

Active Phase* is from M0 to M25
FASI: subjects of the immunogenicity subset who received at least one dose, who had a blood sample drawn and a result available after this dose and who did not have serious non-compliance to GCP.
Dengue seropositive subjects at baseline are defined as subjects with PRNT $_{50}$ titers >= 10 (l/dil) against at least one dengue serotype at baseline. Dengue seronegative subjects at baseline are defined as subjects with PRNT $_{50}$ titers < 10 (l/dil) against all 4 serotypes at baseline.
n= total subjects per sub-group, Dengvaxia or Placebo
Source: Adapted from Original 125682.0; ISE report, Table 3.4.5.38

Clinical Reviewer Comment: *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. Limitations to the analysis include its post-hoc nature and small sample size since only about 10% (1,992/20,869) of subjects had baseline serostatus data collected.*

6.1.12 Safety Analyses

6.1.12.1 Methods

All subjects were assessed for safety (SAEs and AESIs) and a subset of subjects (reactogenicity subset) was assessed for solicited reactions and unsolicited non-serious AEs and ARs. Active surveillance using direct observations, post-dose, and diary cards to record solicited reactions were employed for AEs and ARs. All SAEs and AESIs were determined by investigator evaluation of clinical events and determination of likelihood of being related to study product. Analyses were based on the Safety Analysis Set or Reactogenicity Analysis Set.

6.1.12.2 Overview of Adverse Events

Table 19 shows the safety overview after any dose.

Table 19: Study CYD15, Safety Overview: Safety Outcomes After Any Dengvaxia Dose-Safety Analysis Set

Reactogenicity Subset: Within 28 days any dose	**Dengvaxia M/n (%)**	**Placebo M/n (%)**
Immediate unsolicited non-serious AE	3/1,333 (0.2)	1/664 (0.2)
Immediate unsolicited non-serious adverse reaction (AR)	1/1,333 (<0.1)	1/664 (0.2)
Solicited adverse reactions	994/1,328 (75)	495/659 (75)
Solicited injection site reaction	675/1,328 (51)	279/658 (42)
Solicited systemic adverse reaction	909/1,328 (68)	458/659 (70)
Unsolicited non-serious AE	595/1,333 (47)	292/664 (44)
Unsolicited non-serious AR	16/1,333 (1)	5/664 (0.8)
Unsolicited non-serious injection site AR	9/13,339 (1)	3/664 (0.5)
Unsolicited non-serious systemic AE	592/1,333 (44)	290/664 (44)
Unsolicited non-serious systemic AR	7/1,333 (0.5)	2/664 (0.3)
ALL SUBJECTS	--	--
Within 28 days after any vaccine dose	--	--
AE leading to discontinuation	0/13,915 (0.0)	0/6,939 (0.0)
Immediate SAE	0/13,915 (0.0)	0/6,939 (0.0)
SAE	82/13,915 (0.6)	42/6,939 (0.6)
Death	0/13,915 (0.0)	0/6,939 (0.0)
During the Active Phase (M0 to M25)	--	--
AE leading to discontinuation*	10/13,915 (<0.1)	9/6,939 (0.1)
SAE	571/13,915 (4)	311/6,939 (4.5)
Death	6/13,915 (<0.1)	6/6,939 (<0.1)
During the Hospital Phase/SEP (M25 to M60)	--	--
AE leading to discontinuation*	27/13,296 (0.2)	18/6,644 (0.3)
SAE	1,009/13,296 (7.6)	518/6,644 (7.8)
Death	27/13,296 (0.2)	17/6,644 (0.3)
During the entire study, (M0 to M60)	--	--
AE leading to discontinuation*	37/13,915 (0.3)	27/6,939 (0.4)
SAE	1,494/13,915 (10.7)	790/6,939 (11.4)
Death	33/13,915 (0.2)	23/6,939 (0.3)

M: number of subjects experiencing the safety outcome
n: total number of evaluable subjects in the safety analysis set
Source: Adapted from STN 125682.0; CYD15 Interim Clinical Study Report, Version 4, Table 7.1

Clinical Reviewer Comment: *The frequencies of adverse events were, in general, similar between the two study groups, with higher rates of solicited injection site reactions observed in Dengvaxia group. The percentages of SAEs were lowest within the 28-day period post-vaccination (0.6%) and no deaths occurred during this time period. The percentages of SAEs and deaths increased over time, but the rates were balanced between both groups.*

Solicited local adverse reactions were monitored for 7 days post-vaccination. Systemic adverse reactions were monitored for 14 days post-vaccination.

Table 20 shows the rates of solicited adverse reactions occurring within 7 or 14 days after any dose in the reactogenicity analysis set.

Table 20: Study CYD15, Solicited Adverse Reactions Within 7 or 14 Days After Any Dose - Reactogenicity Analysis Set

Study Group	Dengvaxia Group (N=1333) n/M (%)	Placebo Group (N=664) n/M (%)
Any solicited adverse reaction	994/1,328 (74.8)	495/659 (75.1)
Any grade 3 adverse reaction	195/1,328 (14.7)	76/659 (11.5)
Any injection site reaction*	675/1,328 (50.8)	279/658 (42.4)
Grade 3 injection site reaction	27/1,328 (2.0)	9/658 (1.4)
Pain	650/1,328 (48.9)	270/658 (41.0)
Erythema	83/1,328 (6.3)	44/658 (6.7)
Swelling	77/1,328 (5.8)	27/658 (4.1)
Any systemic adverse reaction†	909/1,328 (68.4)	458/659 (69.9)
Any grade 3 systemic reaction	184/1,328 (13.9)	75/659 (11.4)
Fever	220/1,318 (16.7)	123/654 (18.8)
Headache	727/1,328 (54.7)	379/659 (57.7)
Malaise	536/1,328 (40.4)	261/659 (39.6)
Myalgia	576/1,328 (43.4)	267/659 (40.5)
Asthenia	496/1,328 (37.3)	251/659 (38.1)

N= total number of subjects in the reactogenicity analysis set
n: number of subjects experiencing the endpoint listed in the first column
M: number of subjects with available data for the relevant endpoint
* Solicited injection site reactions were assessed within 7 days after any dose
†Solicited systemic reactions were assessed within 14 days after any injection
Source: Adapted from Original 125682; CYD15 Interim Clinical Study Report, Version 4, Table 7.2

Clinical Reviewer Comment: *There were slightly more grade 3 solicited adverse reactions and any injection site reactions in the Dengvaxia group compared to the placebo control group. The percentage of subjects reporting a systemic adverse reaction, fever or grade 3 systemic adverse reaction was similar between the two study groups. Solicited adverse reactions rates were adequately assessed and the rates of solicited reactions to a normal saline placebo control injection appear to be somewhat higher than typically observed.*

Table 21 shows the solicited systemic adverse reactions within 14 days after each injection in the reactogenicity analysis set.

Table 21: Study CYD15, Solicited Systemic Adverse Reactions Within 14 Days After Each Injection - Reactogenicity Analysis Set

Subjects experiencing at least one:	Dengvaxia Group (N=1,215-1,324) n/M	Dengvaxia Group %	Placebo Group (N=594-657) n/M	Placebo Group %
Fever	--	--	--	--
Post-Dose 1	86/1,264	6.8	42/635	6.6
Post-Dose 2	72/1,228	5.9	42/594	7.1
Post-Dose 3	89/1,215	7.3	52/597	8.7
Grade 3 fever	--	-	--	---
Post-Dose 1	21/1,264	1.7	7/635	1.1
Post-Dose 2	10/1,228	0.8	7/594	1.2
Post-Dose 3	13/1,215	1.1	5/597	0.8
Headache	--	-	--	---
Post-Dose 1	528/1,324	39.9	273/657	41.6
Post-Dose 2	386/1,297	29.8	182/639	28.5
Post-Dose 3	378/1,277	29.6	158/631	25.0
Grade 3 headache	--	--	--	--
Post-Dose 1	67/1,324	5.1	27/657	4.1
Post-Dose 2	27/1,297	2.1	15/639	2.3
Post-Dose 3	33/1,277	2.6	12/631	1.9
Malaise	--	--	--	--
Post-Dose 1	324/1,323	24.5	170/657	25.9
Post-Dose 2	270/1,298	20.8	106/639	16.6
Post-Dose3	246/1,277	19.3	96/631	15.2
Grade 3 malaise	--	--	--	--
Post-Dose 1	32/1,323	2.4	15/657	2.3
Post-Dose 2	17/1,298	1.3	8/639	1.3
Post-Dose 3	18/1,277	1.4	7/631	1.1
Myalgia	--	--	--	--
Post-Dose1	386/1,323	29.2	180/657	27.4
Post-Dose 2	273/1,298	21.0	101/639	15.8
Post-Dose 3	255/1,277	20.0	116/631	18.4
Grade 3 myalgia	--	--	--	--
Post-Dose 1	29/1,323	2.2	10/657	1.5
Post-Dose2	21/1,298	1.6	5/639	0.8
Post-Dose 3	19/1,277	1.5	5/631	0.8
Asthenia	--	--	--	--
Post-Dose 1	326/1,323	24.6	148/657	22.5
Post-Dose 2	231/1,298	17.8	105/639	16.4
Post-Dose 3	208/1,277	16.3	110/631	17.4
Grade 3 asthenia	--	--	---	-
Post-Dose 1	36/1,323	2.7	17/657	2.6
Post-Dose 2	24/1,298	1.8	7/639	1.1
Post-Dose 3	17/1,277	1.3	8/631	1.3

n: number of subjects experiencing the endpoint listed in the first column
M: number of subjects with available data for the relevant endpoint:
Source: Adapted from Original 125682; CYD 15 Interim Study Report, Version 4, Table 7.4

Clinical Reviewer Comment: *The rates of solicited systemic adverse reactions were similar between the Dengvaxia vaccine and control groups. The rates of systemic adverse reactions decreased with each subsequent dose. Headache, myalgia and asthenia were the most commonly observed adverse reactions of any severity and grade 3 headache was the most common grade 3 adverse reaction.*

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 Control Group within 28 days after any injection. Most unsolicited non-serious AEs occurred in the system organ class (SOC) "Infections and infestations" (25.8% and 26.4% in Dengvaxia Group and Control Group, 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 Group and Control Group, 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.

6.1.12.3 Deaths

Active Phase
A total of 12 deaths were reported during the Active Phase, 6 in each study group. None were considered by the study investigator as related to vaccination.

Most deaths were due to accidents and some deaths were due to cancer or a variety of severe diseases that manifested after study enrollment.

HP/SEP
A total of 44 deaths were reported during the HP/SEP 27 in the Dengvaxia Group and 17 in the Control Group. None were considered by the study investigator as related to vaccination. Most deaths were due to accidents and some deaths were due to cancer or a variety of severe diseases that manifested after study enrollment.

Clinical Reviewer Comment: *In the opinion of this reviewer, after reviewing the cause of death for all subjects who died, all deaths in each group were unrelated to the study product or the placebo control product.*

6.1.12.4 Nonfatal Serious Adverse Events

Non-Fatal Serious Adverse Events: Table 22 shows non-fatal serious adverse events for various time intervals in Study CYD15.

Table 22: Study CYD 15, Overview of SAEs - Safety Analysis Set

Subjects experiencing at least one SAE:	Dengvaxia Group (N=13,915) All SAEs n/M (%)	Dengvaxia Group (N=13,915) Related SAEs n/M (%)	Placebo Group (N=6,939) All SAEs n/M (%)	Placebo Group (N=6,939) Related SAEs n/M (%)
Within 28 days after any doses	82/13,915 (0.6)	3/13,915 (0.1)	42/6,939 (0.6)	1/6,939 (<0.1)
Beyond 28 days after any doses	340/13,915 (2.4)	0/13,915 (0.0)	195/6,939 (2.8)	0/6,939 (0.0)
During the 6 months follow-up period	414/13,915 (3.0)	3/13,915 (0.1)	232/6,939 (3.3)	1/6,939 (<0.1)
Beyond the 6 months follow-up period	1147/13,915 (8.2)	0/13,915 (0.0)	596/6,939 (8.6)	0/6,939 (0.0)
During the active phase (until V07)	571/13,915 (4.1)	3/13,915 (0.1)	311/6,939 (4.5)	1/6,939 (<0.1)
During the Year 3 (first year of the hospital phase)	300/13,268 (2.3)	0/13,268(0.0)	165/6,630 (2.5)	0/6,630 (0.0)
During the Year 4 (second year of the hospital phase)	372/13,009 (2.9)	0/13,009(0.0)	201/6,524(3.1)	0/6,524 (0.0)
During the Year 5 (third year of the hospital phase)	410/11,933 (3.4)	0/11,933 (0.0)	198/5,913 (3.3)	0/5,913 (0.0)
During the hospital phase	345/13,287(2.6)	0/13,915 (0.0)	394/14,414 (2.7)	0/12,510 (0.0)
During the SEP	316/8,294 (3.8)	0/489 (0.0)	150/4,093 (3.7)	0/244 (0.0)
During the hospital phase/SEP	1009/13,296 (7.6)	0/13,281 (0.0)	518/6,644 (7.8)	0/6,634 (0.0)
During the entire study	1494/13,915 (10.7)	3/13,915 (<0.1)	790/6,939 (11.4)	1/6,939 (<0.1)

Safety Analysis Set: The safety analysis set is defined for each dose as the subset of subjects who received this dose and who did not have serious non-compliance to GCP. Subjects were analyzed according to the treatment received.
n: number of subjects experiencing the endpoint listed in the column header, M=evaluable subjects for the reporting period
Source: Adapted from STN 125682.0; CYD15 Interim Clinical Study Report, Version 4, Tables 7.1 and 7.7

Clinical Reviewer Comment: *SAEs were balanced between Dengvaxia and Placebo group in each assessed time interval.*

6.1.12.5 Adverse Events of Special Interest (AESI)

Unsolicited non-serious and serious hypersensitivity/allergic reactions occurring within 7 days after any injection were assessed in the reactogenicity analysis set and the safety analysis set, respectively.

Non-serious hypersensitivity/allergic reactions: Seven subjects (4 in the Dengvaxia Group and 3 in the Control Group) experienced at least one non-serious hypersensitivity/allergic reaction AESI within 7 days of any injection.

Serious hypersensitivity/allergic reactions: Five subjects experienced at least one serious AESI (hypersensitivity/allergic reaction) within 7 days of any injection. Four reactions were in the Dengvaxia group and one reaction was in the placebo group. There were no anaphylactic reactions in either group. Each of the serious hypersensitivity/allergic reactions are described below:

Dengvaxia Group:
(1) An 11-year-old male subject experienced asthma 3 days post-injection #2. This subject had a history of asthma. No trigger was identified. This serious AESI required hospitalization and resolved within 4 days of occurrence. Subjects recovered and did not discontinue from further injection. This AESI was assessed as not related to vaccination by the Investigator.

(2) A 9-year-old male subject experienced asthmatic crisis 2 days post-injection #1. The event occurred while the subject had common cold with cough, rhinorrhea, nasal congestion and fever that started 3 days before the first injection. The subject had history of allergic rhinitis and recurrent bronchial obstructive symptoms. This serious AESI required hospitalization and resolved within 36 days. Subject recovered and did not discontinue from further injections. This AESI was assessed as not related to vaccination by the Investigator. (3) An 11-year-old male subject experienced asthma attack 16 hours post-injection #1. This AESI was assessed as related to vaccination by the Investigator. (4) A 14-year-old male subject experienced urticaria 4 hours post-injection #2. This serious AESI was assessed as related to vaccination by the Investigator.

Placebo Group: A 9-year-old male subject experienced asthma 3 days post-injection #1. This subject had history of asthma in the context of bronchitis. This serious AESI required hospitalization and resolved within 2 days of occurrence. Subjects recovered and did not discontinue from further injections. This serious AESI was not assessed as related to vaccination by the Investigator.

Clinical Reviewer Comment: *In the opinion of this reviewer, the two cases assessed as related to Dengvaxia and the one case assessed as related to normal saline placebo control do not constitute a safety signal for this trial. This reviewer concurs with the assessments of relatedness made by the clinical investigators.*

Serious viscerotropic or neurotropic disease: The Dengvaxia vaccine is based upon a YF-17D virus strain. YF vaccination with this strain is known to have rare viscerotropic and neurotropic adverse events, which are more likely to occur in vaccine recipients >50 years of age. Four subjects (3 in the Dengvaxia group and one in the placebo group) developed neurologic symptoms post-vaccination such that serum, cerebrospinal fluid, urine were tested by RT-PCR for presence of Dengvaxia viruses. Descriptions of timing and nature of the presentations included one subjects each with acute polyneuropathy 3 days after the first dose, Leptospirosis diagnosed 2 days after the first dose and seizures several hours after the first dose in the Dengvaxia group and visual impairment 21 hours after first dose in the control group.

Biological specimens collected from these 4 subjects were tested by RT-PCR for alphavirus and flavivirus including for YF virus, and specifically YF-17D, all of which were negative. Overall, no subjects developed any serious viscerotropic or neurotropic diseases within 30 days after any injection.

Clinical Reviewer Comment: *There was no evidence of viscerotropic or neurotropic disease occurrences in this study.*

6.1.12.6 Clinical Test Results

No systematic assessment of biological laboratory parameters was performed in this study. In the context of dengue cases, clinical laboratory evaluations (hematocrit, platelet count, AST and ALT) were performed on subjects presenting with acute febrile illness (i.e., temperature ≥ 38°C on at least 2 consecutive days) in both acute and convalescent specimens. The results of the clinical laboratory examinations in subjects who had dengue disease were consistent with the results normally observed in cases of acute dengue without evidence of DHF. The results of the clinical laboratory examinations for dengue cases with DHF were consistent with the WHO DHF severity classification scheme, with grade 1 and grade 2 of DHF showing reductions in hematocrit and platelet counts and mild elevations of AST and ALT (data not shown).

Clinical Reviewer Comment: *Clinical laboratory abnormalities of hematocrit, platelet count, AST and ALT are common in DHF, and occur to a lesser degree in acute dengue cases without signs of DHF. There were no imbalances in these laboratory analyses between Dengvaxia and control groups and there was no evidence to suggest that subjects with acute dengue in the Dengvaxia group had laboratory abnormalities that would not typically be observed in dengue cases in endemic regions.*

6.1.13 Study Summary and Conclusions

Study CYD15 met the success criterion for the primary efficacy endpoint of symptomatic VCD cases due to any serotype, with an estimated VE of 60.8% (95% CI 52.0; 68.0) (pre-specified success criterion for VE was an LB of the 95%CI of >25%).

In post-hoc exploratory analyses performed only on the 10% immunogenicity subset), VE by serotype varied, with numerically higher VE shown for serotypes 3 and 4. VE also varied by baseline dengue serostatus, with numerically higher estimated VE observed in subjects who were dengue seropositive at baseline,

Most subjects in both Dengvaxia and Placebo treatment groups experienced local and/or general adverse reactions. Most reactions were mild or moderate (grade 1 or grade 2) and no substantial imbalances in severe adverse 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.

6.2 Trial #2: CYD14

Study Title: Efficacy and Safety of a Novel Tetravalent Dengue Vaccine in Healthy Children Aged 2 to 14 years in Asia (NCT 01373281)

Study start date: June 3, 2011 Study Completion date: November 21, 2017

6.2.1 Objectives (Primary and Secondary)

Primary Objective: To assess the efficacy of Dengvaxia vaccine after 3 vaccinations at 0, 6 and 12 months in preventing symptomatic VCD cases, regardless of severity, due to any of the 4 dengue serotypes in children 2 through 14 years of age (same as study CYD15).

Secondary Objectives: The secondary objectives for safety and immunogenicity (described in Section 6.1.1) in this study were the same as study CYD15.

Other Objectives: Relationship between neutralizing antibody levels and VE: To describe the relationship between post-Dose #3 neutralizing antibody level ($PRNT_{50}$ assay) and the subsequent occurrence of symptomatic dengue cases.

6.2.2 Design Overview

Study CYD14 was a phase 3 clinical endpoint efficacy trial conducted in five Asia-Pacific countries in 2 through 14-year-old subjects, and enrolled a total of 10,275 subjects, randomized 2:1 to receive either Dengvaxia or placebo group.

The majority of the CYD14 study design elements were the same as for study CYD15 with respect to the following:

- vaccination schedule;
- control group received saline placebo;
- primary efficacy endpoint;
- case definition for VCD, management of suspected dengue cases, duration of efficacy follow-up in the Active Phase and follow up for severe/hospitalized dengue in the HP, re-consenting all willing subjects for the SEP during the fourth year of the study (which was the second year of the HP) and resuming active surveillance for symptomatic VCD cases as well as continuation of active surveillance for severe/hospitalized dengue through second, third and fourth years of HP (refer to Figure 1 for schematic diagram of the phases of the study);
- secondary objectives and corresponding endpoints;
- eligibility criteria;
- randomization and blinding procedures;
- blood samples obtained for the immunogenicity subset and overall study population;
- safety evaluations; and
- study success criterion, definitions of the statistical analysis sets, efficacy, safety (including reactogenicity) and immunogenicity analyses.

Key differences between the CYD14 and CYD15 study designs were:

- Study population: CYD14 enrolled subjects ages 2 through 14 years, whereas CYD15 enrolled subjects ages 9 through 16 years.
- Location: CYD14 enrolled subjects from 5 countries in the Asia-Pacific region, whereas CYD15 enrolled subjects from Central America, South America, and Puerto Rico.
- Sample size: CYD14 enrolled a total of 10,275 subjects, whereas CYD15 enrolled a total of 20,869 subjects.
- Except for additional surveillance via school absenteeism follow-up during the Active Phase, planned duration and surveillance during the Active Phase, HP and SEP in this study were the same as for study CYD 15.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Identical to study treatments mandated by protocol for CYD15. See Section 6.1.4

6.2.5 Directions for Use

Identical to directions for use for CYD15. See Section 6.1.5

6.2.7 Surveillance/Monitoring

Identical to surveillance monitoring for CYD15. See Section 6.1.7

6.2.8 Endpoints and Criteria for Study Success

Identical to Study CYD15. See Section 6.1.8.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Sample size:
Efficacy: Planned enrollment included a total of 10,278 subjects (6852 subjects and 3526 subjects in Dengvaxia and Control groups, respectively). Assuming an alpha of 2.5% (one-sided hypothesis), a yearly incidence of symptomatic VCD cases of 1.3%, an overall drop-out from the PPSE set of 20%, and a true VE of 70% after Dose 3, a total of 57 confirmed dengue cases was expected during the 12-month active follow-up, providing > 90% power to show a significant efficacy (LB of the 95% CI > 25%) using the exact method.

The estimated VE for the FASE population (with at least one dose of Dengvaxia) at the end of the active follow-up was assumed to be 55%. The expected number of dengue cases identified in the FASE was approximately 161 (occurring 28 days post-Dose 1 until the end of the Active Phase, month 25). Based on the planned sample size, there was at least 87% power to conclude that the LB of the point estimate for VE on the FASE population was > 25% (i.e., the pre-specified success criterion for efficacy). Because analysis of VE beyond the Active Phase was descriptive, no statistical assumptions were made for VE for the SEP or for the whole length of the trial.

Reactogenicity: Planned enrollment of subset included a total of 2,000 subjects (1333 subjects and 667 in Dengvaxia and Control Groups, respectively). 1333 subjects in the Dengvaxia group gave a 95%probability of observing an event with a true incidence of 0.23%.

Between 300 and to 600 subjects were targeted to be enrolled in each participating country.

Immunogenicity: The same subset as for reactogenicity was used for the immunogenicity evaluation. Statistical analyses of immunogenicity were descriptive.

Analysis for the Primary Objective
The primary efficacy analysis was based on the PPSE (for descriptions of analysis groups see section 6.2.10 below). Only the first VCD case occurring after 28 days post-Dose #3 was considered for the analysis of the primary objective (i.e., if the same subject has a second case of VCD during the study this was not included as an additional case for efficacy analysis). Also, a secondary analysis of VE was also performed on the mFASE population. Additional secondary analyses were conducted to evaluate for differences related to locality and other covariates that might impact effectiveness. The statistical methodology was based on the use of the two-sided 95% CI of the estimated VE. The CI was calculated using the exact method conditional on the total number of cases in both groups.

The following hypotheses (H) were tested using an alpha=2.5% H0: VE ≤ 25%
H1: VE > 25%

Two-sided 95% CIs of the VE were calculated using the exact method described by Breslow & Day. Groups described by Breslow & Day.

The efficacy estimate given above may be restated as VE = 100 * [1 – N_P/N_{CYD} * q/(1–q)], where *q* is the proportion of cases who received Dengvaxia. Thus, [q/(1-q)] is equivalent to [Dengvaxia /Control]. Conditionally to the total number of cases, $C_{Dengvaxia}$ has a binomial distribution (*q*,$C_{Dengvaxia}$+$C_{Control}$). Thus, a CI for *q* may be constructed using the exact Clopper Pearson method for binomial proportions.

Efficacy analyses for the secondary and other objectives:
Analyses were descriptive and without pre-specified success criteria. However, secondary efficacy, immunogenicity, and safety parameters were described with 95% CI using normal assumption for quantitative data, exact binomial distribution for proportions (Clopper-Pearson method) and exact method (Breslow & Day) for VE.

Relationship between neutralizing Ab levels and the occurrence of dengue disease:
At the minimum, serum samples from subjects with a virologically-confirmed dengue case and serum samples from all subjects from the immunogenicity and reactogenicity subset were used to investigate a correlate of protection.

Clinical Reviewer Comment: *CBER agreed with the SAP.*

6.2.10 Study Population and Disposition

6.2.10.1 Populations Enrolled/Analyzed

Between 03 June 2011 and 01 December 2011, a total of 10,278 subjects were enrolled (3 subjects were randomized twice). A total of 10,275 subjects were randomized: 6,851 were randomized to the Dengvaxia Group and 3,424 to the Control Group. Between June 2011 and October 2011, 2,000 subjects (1,336 subjects and 664 subjects in the Dengvaxia and Control Groups, respectively) were randomized to the immunogenicity and reactogenicity subset. The distribution by country and treatment group of all subjects randomized to the study for this subset is summarized in Table 23.

Table 23: Study CYD14, Country Distribution and Randomized Treatment Group in the Overall Population and in the Immunogenicity & Reactogenicity Subset - Randomized Subjects

Country/Number of Sites	Dengvaxia Group (N=6,851) M/n (%)	Placebo Group (N=3,424) M/n (%)	Total (N=10,275) M/n (%)
Indonesia/8	234/1,246 (18%)	116/624 (18%)	350/1,870 (18%)
Malaysia/5	204/937 (14%)	96/464 (14%)	300/1,401 (21%)
Philippines/4	402/2,335 (34%)	200/1,166 (34%)	602/3,501 (17%)
Thailand/2	255/788 (11%)	116/392 (11%)	341/1,170 (29%)
Vietnam/4	271/1,555 (23%)	136/778 (23%)	407/2,333 (17%)

M: number of subjects enrolled at each site, n(%): number and percent of subjects in immunogenicity/reactogenicity subset
Source: Adapted from STN 125682.0; Clinical Study Report CYD14, Version 4; Table 4.4

Overall, 10,194 subjects (99.2%) completed the Active Phase of the study. At Visit 10 (Planned Y2 of HP, Year 4 of the study, i.e., 36 months after the third vaccination), 10,089 (98.2%) of all subjects randomized at the beginning of the study re-consented for enrollment in the SEP. At Visit 11 (Y3 of HP/SEP, Year 5 of the study; i.e., 48 months after the third vaccination), 9917 (96.5%) completed the 3-year HP/SEP.

The same percentage was observed in the subset (99.2% and 97.0%, respectively for the Active Phase and the 3-year HP/SEP).

A total of 10,272 subjects (3 were not vaccinated) were included in the FASE; 10,059 subjects were included in the PPSE; and 10,272 were included in the mFASE.

Clinical Reviewer Comment: *This study was not powered to evaluate efficacy by individual country. The Philippines were over-represented in the study and Thailand was under-represented in the study. However, the phase 2, Study CYD23, (see section 6.3) was conducted solely in Thailand in 4,002 subjects 4-11 years of age, providing additional representation for that country in the overall Asian population. CYD 14 was conducted in Asia-Pacific to provide data from that dengue endemic region of the world and the plan to conduct studies in different dengue endemic regions of the world is consistent with WHO recommendations for evaluation of a preventive dengue vaccine. A major limitation of CYD14, as with CYD15 (see Section 6.1) is that there was insufficient enrollment in individual countries to provide statistically significant findings per country. This is an acceptable limitation given that dengue disease varies primarily as a function of first versus second, heterologous infections, in terms of severity, and the primary objective of this vaccine is to prevent dengue cases from any serotype. Protection against any dengue case from any serotype is a clinical benefit and it was not feasible to power the study for efficacy per serotype due to the unpredictable nature of dengue serotype circulation, year to year; nor was it feasible to power the study per country given the objective of assessing efficacy by region of the dengue-endemic world with CYD 15 for South America and CYD 14 for the Asia Pacific region.*

6.2.10.1.1 Demographics
In Trial CYD14 the percentage of subject enrollment per country was:
Philippines (34%); Vietnam (23%); Indonesia (18%); Malaysia (14%) and Thailand (11%).

The percentage enrollment by age sub-group was:
2-5 years (24%); 6-11 years (53%); 12-14 years (23%) and 9-14 years (49%).

Females comprised 51.5% of the total randomized population. All subjects identified as “Asian” by ethnicity and “white” by race.

6.2.10.1.2 Medical/Behavioral Characterization of the Enrolled Population

No identifiable medical or behavioral characteristics for the study population were collected.

Clinical Reviewer Comment: *There were no identifiable medical or behavioral characteristics identified for the study population that were likely, in this reviewer’s opinion, to affect the interpretation of the study’s efficacy, immunogenicity or safety results. A behavioral characteristic that could have impacted the study results would have been any personal protection measures or vector control strategies that would have impacted the likelihood of exposure to potentially infectious mosquito bites, however such measures are not systematically employed in dengue endemic regions and any incidental measures were assumed to be evenly distributed at these clinical study sites.*

6.2.10.1.3 Subject Disposition
Figure 3 shows subjects disposition.

Figure 3. Study CYD14. Subject Disposition

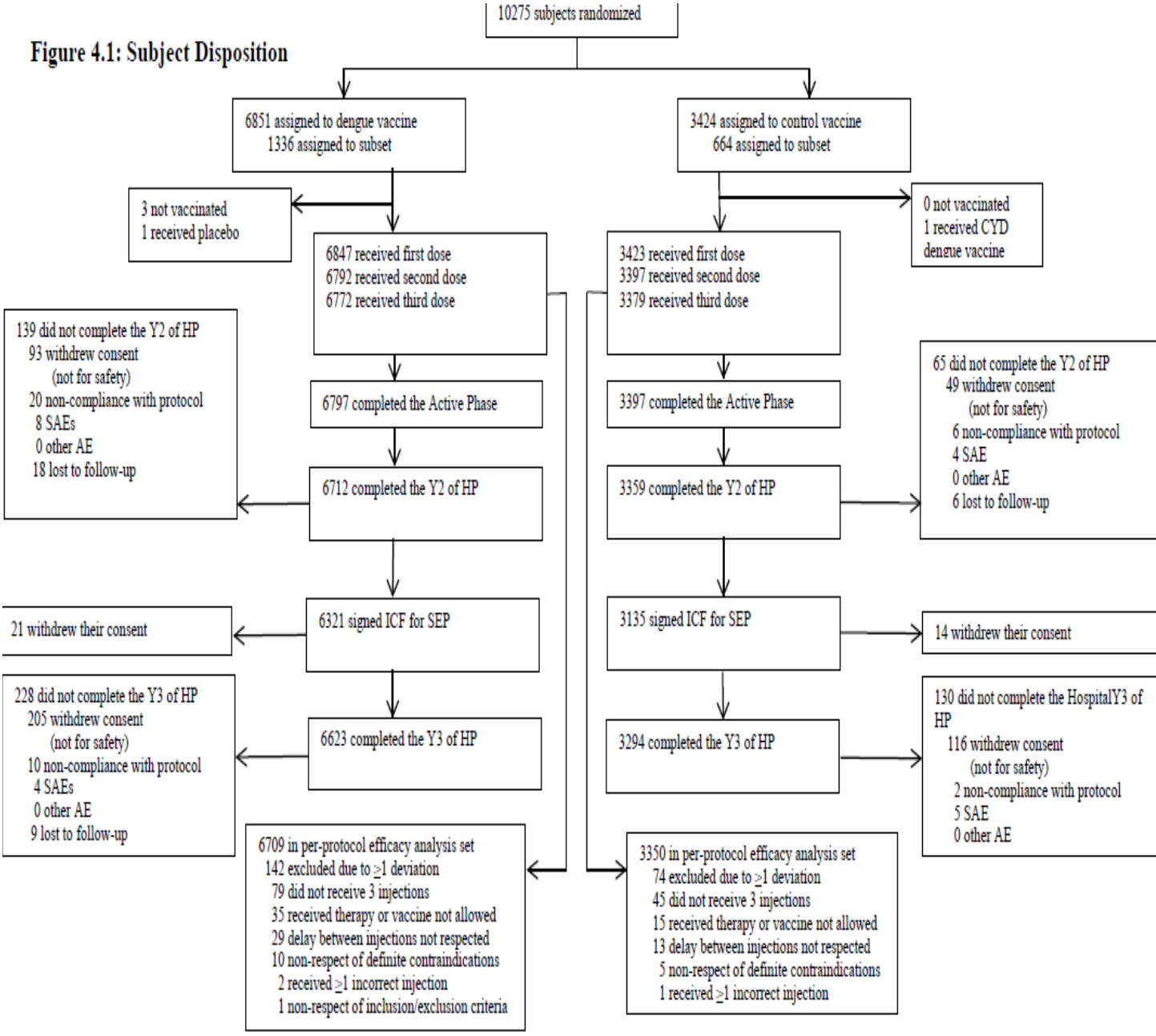


Table 24 shows the percentage of subjects who completed the study at various timepoints.

Table 24: Study CYD14, Subject Completion or Termination from Study

Disposition by visit number (study timepoint)	Dengvaxia Group (N=6,851) n (%)	Control Group (N=3,424) n (%)	All Subjects (N=10,275) n (%)
V06 (28 days post 3rd vaccination)	--	--	--
Completed vaccination period	6,772 (98.8)	3,379 (98.7)	10,151 (98.8)
Early termination	79 (1.2)	45 (1.3)	124 (1.2)
Reason	--	--	--
SAE	6 (0.1)	5 (0.1)	11 (0.1)
Other AEs*	4 (0.1)	4 (0.1)	8 (0.1)
Non-compliance with protocol	13 (0.2)	4 (0.1)	17 (0.2)
Lost to follow-up	4 (0.1)	1 (0.0)	5 (0.0)
Voluntary withdrawal not for adverse event	52 (0.8)	31 (0.9)	83 (0.8)
Decision made by Investigator	27 (0.4)	13 (0.4)	40 (0.4)
Subject or legal representative	52 (0.8)	32 (0.9)	84 (0.8)
V07 (last vaccination plus 13 mos.)	--	--	--
Contacted 13 months after the last	6,797 (99.2)	3,397 (99.2)	10,194 (99.2)
Not contacted	54 (0.8)	27 (0.8)	81 (0.8)
Reason	--	--	--
SAE	4 (0.1)	1 (0.0)	5 (0.0)
Other AEs*	0 (0.0)	0 (0.0)	0 (0.0)
Non-compliance with protocol	5 (0.1)	2 (0.1)	7 (0.1)
Lost to follow-up	5 (0.1)	1 (0.0)	6 (0.1)
Voluntary withdrawal not for adverse event	40 (0.6)	23 (0.7)	63 (0.6)
V09 (last vaccination plus 24 mos.)	--	--	--
Contacted 24 months after the last	6,763 (98.7)	3,380 (98.7)	10,143 (98.7)
Not contacted**	88 (1.3)	44 (1.3)	132 (1.3)
Reason	--	--	--
SAE	5 (0.1)	1 (0.0)	6 (0.1)
Other AEs*	0 (0.0)	0 (0.0)	0 (0.0)
Non-compliance with protocol	10 (0.1)	3 (0.1)	13 (0.1)
Lost to follow-up	10 (0.1)	5 (0.1)	15 (0.1)
Voluntary withdrawal not for adverse event	63 (0.9)	35 (1.0)	98 (1.0)
V10 (last vaccination plus 36 mos.)	--	--	--
Completed until V10	6,712 (98.0)	3,359 (98.1)	10,071 (98.0)
Early termination	139 (2.0)	65 (1.9)	204 (2.0)
Reason	--	--	--
SAE	8 (0.1)	4 (0.1)	12 (0.1)

Other AEs*	0 (0.0)	0 (0.0)	0 (0.0)
Non-compliance with protocol	20 (0.3)	6 (0.2)	26 (0.3)
Lost to follow-up	18 (0.3)	6 (0.2)	24 (0.2)
Voluntary withdrawal not for adverse event	93 (1.4)	49 (1.4)	142 (1.4)
Decision made by investigator	45 (0.7)	16 (0.5)	61 (0.6)

n: number of subjects fulfilling the item listed
* Discontinuations for other AEs may not be considered for the safety analysis if intensity is < Grade 1 according to the Sponsor
** Subjects who refused to sign ICF/AF addendum for 2-year follow-up extension are reported as discontinued for voluntary withdrawal at V11
† Derived variable using data collected at V10 and V11
Source: Adapted from STN 125682.0; Clinical Study Report CYD14, Version 4, Table 10.2

Clinical Reviewer Comment: *There was a very high level of compliance with the per protocol vaccinations in both Dengvaxia vaccine and normal saline placebo groups. Withdrawals due to SAEs, and AEs; non-compliance with study protocol and loss to follow-up were minimal in both Dengvaxia vaccine and placebo control groups. In the opinion of this reviewer, these characteristics of study completion do not introduce any imbalance between groups that would affect interpretation of the study results.*

6.2.11 Efficacy Analyses

Efficacy analyses are presented by primary and secondary endpoints for the entire randomized population, 2 through 14 years of age and in exploratory analyses by age sub-groups.

6.2.11.1 Analyses of Primary Endpoint(s)

The primary efficacy endpoint was the occurrence of symptomatic, virologically-confirmed dengue cases of any serotype during the active surveillance period of 12 months from the time point 28 days post dose #3.

Table 25 shows the per protocol set for efficacy results. The primary success criterion was met, as the lower bound of 95% CI of the VE was above 25%.

Table 25: Study CYD14, Efficacy Against Symptomatic, Virologically-Confirmed Dengue Post-Dose #3, Due to Any Vaccine Serotype, in Subjects 2 Years to 14 Years of Age – Per-Protocol Analysis Set for Efficacy (PPSE)

	Dengvaxia Group (N=6,709)	**Placebo Group (N=3,350)**	**VE (95%CI)**
Symptomatic, Virologically Confirmed Dengue Cases	117	133	**56.5%** (43.8;66.4)

Cases: number of subjects with at least one symptomatic virologically-confirmed dengue episode from 28 days post-dose 3 to the end of Active Phase.
The VE is considered as significant if the lower bound of its 95% CI was greater than 25%.
Source: Adapted from STN 125682.0; Clinical Study Report CYD14, Version 4, Table 5.1

Clinical Reviewer Comment: *A total of 250 subjects reported at least 1 VCD episode in the 12 months between 28 days post-dose #3 and the end of the Active Phase. The overall primary estimate of VE against symptomatic VCD post-Dose 3 due to any serotype including all subjects*

2 through 14 years of age, by the PPSE was 56.5% (95% CI: 43.8; 66.4). The study success criterion was met, as the lower bound of 95% CI of the VE was above 25%. Similar results were observed in the mFASE (not shown). This reviewer makes note that the VE estimate and LB of the 95%CI's are higher in the FASE sub-population analyses that include only 9 through 14 year-old subjects and in analyses that include only subjects who were dengue seropositive pre-vaccination (see Tables 30 and 31, Section 6.2.11.5; and Section 7, Overview Of Efficacy).

6.2.11.2 Analyses of Secondary Endpoints

Efficacy
VE by Serotype:

VE against VCD due to any and each serotype 28-days post-Dose 3 (i.e., months 13 to 25, the time frame for which primary efficacy endpoint was evaluated) and during the Active Phase (month 0 to 25) are summarized in Table 26 below.

Table 26: Study CYD14. Vaccine Efficacy Against VCD Cases Post-dose #3, Due to Any and Each Dengue Serotype; modified Full Analysis Set for Efficacy for Post-Dose 3 and Full Analysis Set for Efficacy for Active Phase

Serotype	Number of cases Dengvaxia vs Placebo	VE % (95% CI)	Number of cases Dengvaxia vs Placebo	VE % (95% CI)
Any serotype	118/134	**56.5** (44;66)	286/309	**54.8** (47;62)
Serotype 1	51/50	**50.0** (25;67)	116/126	**54.5** (41;65)
Serotype 2	38/29	**35.0** (-9;61)	97/74	**34.7** (10;52)
Serotype 3	10/23	**78.4** (53;91)	30/43	**65.2** (43;79)
Serotype 4	17/34	**75.3** (55;87)	40/72	**72.4** (59;82)

Cases: number of subjects with at least one symptomatic VCD episode in the considered period.
[1]Post-Dose 3: period from 28 days post-Dose 3 to the end of the Active Phase (mFASE)
[2]Active Phase: period from Month 0 to Month 25
Source: Adapted from STN 125682.0; Clinical Study Report CYD14, Version 4, Table 5.2

Clinical Reviewer Comment: *During the Active Phase, descriptive analyses by serotype showed different VE point estimates ranging from 34.7% (serotype 2) to 72.4% (serotype 4). Such serotype-specific differences in efficacy were predicated by the results from phase 2 study, CYD23, (see Section 6.3 of the clinical review) conducted prior to the two phase 3 clinical efficacy endpoint studies (CYD15 and CYD14). These serotype-specific differences in efficacy were consistent and of the same pattern in all three clinical efficacy endpoint studies. The immune responses to Dengvaxia vaccination do not explain these differences in efficacy by serotype (see Table 27, below) as the PRNT50 GMTs post dose 3 were higher for serotype 2 than for serotypes 1, 3 and 4. This study was not powered to assess serotype-specific efficacy and these results are descriptive.*

Immunogenicity

Dengue GMTs by dengue serostatus at baseline (pre-vaccination #1), assessed in an exploratory analysis, are shown in Table 27.

Table 27: Study CYD14, GMTs of Dengue Antibodies Against Each Serotype with the Parental Dengue Virus Strains, by Dengue Serostatus at Baseline – FASI

Serotype and Timepoint	Dengue Seropositive Dengvaxia Group (N= 1,323, M=887-891) GMT (95%CI)	Dengue Seropositive Placebo Group (N=660, M=437-443) GMT (95%CI)	Dengue Seronegative Dengvaxia Group (N=1323, M=417-419) GMT (95%CI)	Dengue Seronegative Placebo Group (N=660, M=210-212) GMT (95%CI)
Serotype 1 Pre-Dose 1	101 (87;117)	119 (96;148)	5 (NC)	5 (NC)
Serotype 1 Post-Dose 3	300 (267;338)	118 (94;146)	47 (41;54)	6 (6;8)
Serotype 2 Pre-Dose 1	172 (151;197)	212 (176;255)	5 (NC)	5 (NC)
Serotype 2 Post-Dose 3	556 (507;610)	202 (167;244)	137 (121/156)	7 (6;9)
Serotype 3 Pre-Dose 1	107 (94;123)	113 (95;135)	5 (NC)	5 (NC)
Serotype 3 Post-Dose 3	339 (305;376)	102 (85;122)	72 (65;82)	7 (6;8)
Serotype 4 Pre-Dose 1	55 (48;61)	59 (50;70)	5 (NC)	5 (NC)
Serotype 4 Post-Dose 3	206 (189;223)	50 (42;59)	77 (70;87)	7 (6;8)

N: number of subjects in the FASI, M: number of subjects available for the endpoint, NC: not calculatable
Dengue seronegative subjects at baseline are defined as subjects with titers < 10 (l/dil) against all 4 serotypes at baseline (undetectable titers imputed to 5).
Dengue seropositive subjects at baseline are defined as subjects with titers >= 10 (l/dil) against at least one dengue serotype at baseline.
Source: Adapted from STN 125682.0; Clinical Study Report CYD14, Version 4, Table 6.4.

Clinical Reviewer Comment: *In the Dengvaxia group, subjects who were dengue seropositive at baseline developed higher post-dose-3 GMT's than subjects who were dengue seronegative at baseline. Although a post-vaccination GMT level associated with protection from dengue disease was not identified in this or other studies evaluating Dengvaxia, a general trend was observed between higher post-vaccination GMTs and higher rates of protection. Thus lower-post-vaccination GMTs in subjects who were dengue seronegative at baseline (compared to subjects who were dengue seropositive at baseline) might have contributed to numerically lower VE estimates observed in subjects who were dengue seronegative at baseline. Of note, this was an exploratory analysis and is limited to 10% of subjects who were in the immunogenicity subset.*

6.2.11.3 Subpopulation Analyses

Table 29 shows VE against any serotype by age sub-group, by dengue serostatus at baseline and by country. These were each exploratory, post-hoc analyses and there were no pre-specified success criteria on these endpoints.

Table 29. Study CYD14, Vaccine Efficacy or Relative Risk Against Any Serotype During the Active Phase by Age Strata, Dengue Dengue Serostatus at Baseline, and Country-FASE

Parameter	Dengvaxia Group Cases/Person-Years at Risk	Placebo Group Incidence Density (95% CI)	Placebo Group Cases/Person-Years at Risk	Placebo Group Incidence Density (95% CI)	Vaccine efficacy % (95% CI)
Age strata	--	--	--	--	--
2 to 5 years	120/3,219	3.7 (3.1; 4.4)	89/1,584	5.6 (4.5; 6.9)	**33.7** (11.7; 50.0)
6 to 11 years	137/7,229	1.9 (1.6; 2.2)	165/3,528	4.7 (4.0; 5.4)	**59.5** (48.9; 68.0)
12 to 14 years	29/3,123	0.9 (0.6; 1.3)	55/1,515	3.6 (2.7; 4.7)	**74.4** (59.2; 84.3)
Dengue Serostatus at Baseline	--	--	--	--	**Relative Risk for dengue case (95% CI)**
Dengue Seropositive*	18/1,811	1.0 (0.6; 1.6)	34/880	3.9 (2.7; 5.4)	**0.257** (0.14; 0.47)
Dengue Seronegative**	23/838	2.7 (1.7; 4.1)	18/423	4.3 (2.5; 6.6)	**0.646** (0.33; 1.27)
Country	--	--	--	--	**Vaccine efficacy % (95% CI)**
Indonesia	40/2,431	1.6 (1.2; 2.2)	43/1,195	3.6 (2.6; 4.8)	**54.3** (28.0; 71.0)
Malaysia	9/1,861	0.5 (0.2; 0.9)	21/910	2.3 (1.4; 3.5)	**79.0** (52.3; 91.5)
Philippines	143/4,618	3.1 (2.6; 3.6)	150/2,232	6.7 (5.7; 7.8)	**53.9** (41.7; 63.6)
Thailand	44/1,529	2.9 (2.1; 3.8)	45/753	6.0 (4.4; 7.9)	**51.8** (25.3; 68.9)
Vietnam	50/3,132	1.6 (1.2; 2.1)	50/1,532	3.3 (2.4; 4.3)	**51.1** (26.1; 67.6)

Cases: number of subjects with at least one symptomatic VCD episode during the Active Phase.
Incidence density: data are cases per 100 person-years at risk.
* Dengue seropositive subjects at baseline are defined as subjects with titers ≥ 10 (l/dil) against at least one dengue serotype at baseline.
**Dengue seronegative subjects at baseline are defined as subjects with titers < 10 (l/dil) against all 4 serotypes at baseline.
Source: Adapted from STN 125682.0; Clinical Study Report CYD14, Table 5.10, 5.12 and 5.14

Clinical Reviewer Comment: *There were trends towards increased VE with increasing age observed in CYD14 study. Subjects who were dengue seropositive at baseline had substantially lower RR of symptomatic VCD compared to dengue seronegative subjects. By country, the VE in Malaysia was higher than the other four countries due, at least in part, to 52.8% of Dengvaxia subjects being dengue seropositive at baseline compared to 37.2% of*

Placebo subjects who were dengue seropositive at baseline (see Table 28); whereas in the other four countries the percentage of dengue seropositive at baseline was similar in Dengvaxia and Placebo groups. These data show how age of exposed subjects and dengue serostatus at baseline may influence effectiveness for a given country during a given period.

6.2.11.5 Exploratory and Post Hoc Analyses

Exploratory, post-hoc analyses were conducted to evaluate efficacy by age sub-group; by dengue serostatus at baseline; and by GMTs for cases and non-cases. Table 30 shows VE against any serotype by the age groups 2-14 years and 9-14 years and Table 31 shows VE against any serotype by dengue serostatus at baseline in subjects 9-14 years.

Table 30: Study CYD14, Vaccine Efficacy Against Symptomatic Virologically-Confirmed Dengue Post-Dose 3 Due to Any of the 4 Serotypes in Subjects 2–14 Years of Age (PPSE[1]) and 9–14 Years of Age - FASE[2]

Treatment group	Cases[3]	Number of episodes	VE %[4] (95% CI)
Dengvaxia (PPSE) Ages 2 -14 years N[5] = 6,709	117	117	**56.5** (43.8, 66.4)
Placebo (PPSE) Ages 2 -14 years N = 3,350	133	134	--
Dengvaxia (FASE) Ages 9 -14 years N = 3,286	13	13	**69.6** (36.3, 86.0)
Placebo (FASE) Ages 9 -14 years N = 1,466	21	21	--

[1]PPSE = Per protocol analysis set for efficacy; this was a pre-specified analysis
[2]FASE = Full analysis set for efficacy, cases were counted after the first dose; this was a post-hoc analysis with no success criteria pre-specified.
[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 for the PPSE, 2-14 years
[5]N = Number in treatment group, PPSE
Source: Adapted from STN 125682/0 Clinical Study Report for CYD14 Table 5.1

Clinical Reviewer Comment: *VE varied by age grouping with higher VE point estimate of 69.6% in individuals 9 through 14 years of age by the FASE compared to 56% for the entire study, in individuals 2 through 14 years of age by the PPSE.*

Table 31: Study CYD14, VE Against Virologically-Confirmed Dengue Cases Post-dose 3 Due to Any of the 4 Serotypes, by Baseline Dengue Dengue Serostatus, Subjects 9 Through 14 Years of Age – FASE[1]

Treatment Group by Baseline Immune Status	Dengue Seropositive Dengvaxia Group	Dengue Seropositive Placebo Group	Dengue Seronegative Dengvaxia Group	Dengue Seronegative Placebo Group
Number of subjects	487	251	129	59
Number of cases	7	17	7	8
VE % (95% CI)		**79.2** (47.2; 97.7)		**61.6** (-21.1; 88.1)

[1]FASE = Full analysis set for efficacy, cases were counted after the first dose
Cases: number of subjects with at least one symptomatic virologically-confirmed dengue episode.
Source: Adapted from STN 125682.0; ISE, Table 3.6.5.15

Clinical Reviewer Comment: *Vaccine efficacy varied as a function of dengue serostatus at baseline. The post dose 3, PRNT50 GMTs, as a function of dengue serostatus pre-vaccination, (refer to Table 27) support an assertion that the Dengvaxia vaccine is weakly immunogenic in the absence of a prior dengue infection and that this is related to the decreased efficacy of the vaccine in dengue seronegative individuals at baseline. This finding supports the efficacy of Dengvaxia in the age group included in the requested indication for this vaccine for individuals who have serological evidence of a prior dengue infection.*

Relationship Between Neutralizing Ab Levels and VE: Table 32 shows the GMTs in cases and non-cases by the mFASE.

Table 32: Study CYD14, GMTs of Dengue Antibodies Against Each Serotype with the Parental Virus Strains for Dengue Cases and Non-Cases, Post-Dose 3 - mFASE[1]

	Dengvaxia Group (N=6,772)						Placebo Group (N=3,379)					
Post-Dose 3	**Cases**			**Non-cases**			**Cases**			**Non-cases**		
Serotype	**M**	**GMT**	**(95% CI)**	**M**	**GMT**	**(95% CI)**	**M**	**GMT**	**(95% CI)**	**M**	**GMT**	**(95% CI)**
Serotype 1	50	58.1	(41.9; 80.4)	1,275	167	(150; 185)	47	11.8	(8.07; 17.2)	604	44.7	(36.8; 54.3)
Serotype 2	36	129	(92.5; 179)	1,273	352	(324; 382)	26	23.8	(12.6; 45.0)	604	61.8	(51.3; 74.6)
Serotype 3	10	77.5	(49.6; 121)	1,273	208	(190; 228)	23	22.7	(14.0; 36.6)	604	40.0	(33.8; 47.3)
Serotype 4	17	61.7	(32.9; 116)	1,274	150	(140; 161)	34	13.7	(8.85; 21.1)	604	24.3	(21.1; 28.0)

[1]mFASE: subjects who received all three doses, analysis based on GMTs 28 days post-dose 3
M: number of subjects with available data for the relevant endpoint.

Cases are subjects with at least one symptomatic VCD case between 28 days post-Dose 3 and the end of the Active Phase due to the considered serotype.
Non-cases are subjects in the FASI who do not have VCD due to any serotype between Visit1 and the end of the Active Phase.
Source: Adapted from STN 125682.0; Clinical Study Report CYD14, Version 4, Table 6.5

Clinical Reviewer Comment: *In the Dengvaxia vaccine group, the non-cases had substantially higher PRNT50 GMTs compared to the cases. Although there was no GMT that was predictive of protection, there was a tendency towards higher VE with higher post-dose-3 GMTs.*

6.2.12 Safety Analyses

6.2.12.1 Methods

Please refer to Sections 6.1.12.1 for a description of the safety analysis methods.

6.2.12.2 Overview of Adverse Events

Table 33 shows the overview of Safety after any injection by the FASS.

Table 33: Study CYD14. Safety Overview After Any Dose - FASS

Subjects experiencing at least one:	**Dengvaxia Group**	**Placebo Group**
Safety Analysis Set (Active Phase)	**N=6,848**	**N=3,424**
SAE*, n (%)	355 (5.2)	220 (6.4)
Death, n (%)	4 (<0.1)	1 (<0.1)
Safety Analysis Set (HP/SEP)	**N=6,782**	**N=3,387**
SAE*, n (%)	517 (7.6)	294 (8.7)
Death, n (%)	3 (<0.1)	3 (<0.1)
Reactogenicity Subset	**N=1,334**	**N=663**
mmediate unsolicited non-serious AE, n (%)	0 (0)	0 (0)
Solicited reactions, n (%)	896 (67.3)	423 (63.8)
Solicited injection site reaction†, n (%)	633 (47.5)	285 (43.0)
Solicited systemic reaction†, n (%)	760 (57.1)	367 (55.4)
Unsolicited non-serious AE, n (%)	489 (36.7)	268 (40.4)
Unsolicited non-serious AR, n (%)	19 (1.4)	6 (0.9)
Unsolicited non-serious injection site AR, n (%)	9 (0.7)	2 (0.3)
Unsolicited non-serious systemic AE, n (%)	489 (36.7)	268 (40.4)
Unsolicited non-serious systemic AR, n (%)	10 (0.7)	4 (0.6)

N: number of subjects in the specified analysis set

*This includes SAEs due to VCD

†Data missing for 2 subjects in the Dengvaxia Group

Source: Adapted from STN 125682.0; Clinical Study Report CYD14, Version.4, Table 7.1

Clinical Reviewer Comment: *The percentage of subjects with any SAE, death, and solicited and un-solicited AEs was similar between the Dengvaxia and Placebo groups.*

Table 34 shows the solicited adverse reactions by type and grade in CYD14.

Table 34: Study CYD14, Solicited Adverse Reactions Within 7 or 14 Days After Any Dose - Reactogenicity Analysis Set

Subjects experiencing at least one:	Dengvaxia Group n/M	Dengvaxia Group %	Placebo Group n/M	Placebo Group %
Solicited reaction	896/1,332	67.3	423/663	63.8
Grade 3 solicited reaction	75/1,332	5.6	29/663	4.4
Solicited injection site reaction	633/1,332	47.5	285/663	43.0
Pain	614/1,332	46.1	275/663	41.5
Grade 3 pain	1/1,332	<0.1	0/663	0
Erythema	107/1,332	8.0	52/663	7.8
Grade 3 Erythema	0/1,332	0	0/663	0
Swelling	68/1,332	5.1	33/663	5.0
Grade 3 Swelling	0/1,332	0	0/663	0
Grade 3 injection site reaction	1/1,332	<0.1	1/663	0.2
Solicited systemic reaction	760/1,332	57.1	367/663	55.4
Fever	248/1,332	18.6	118/663	17.8
Grade 3 Fever	18/1,330	0.013	7/663	<0.1
Headache	562/1,332	42.2	259/663	39.1
Grade 3 Headache	7/1,332	0.5	6/663	0.6
Malaise	476/1,332	35.7	239/663	36.0
Grade 3 Malaise	7/1,332	0.5	4/663	0.6
Myalgia	414/1,332	31.1	197/663	29.7
Grade 3 Myalgia	2/1,332	0.5	2/663	0.6
Asthenia	378/1,332	28.4	167/663	25.2
Grade 3 Asthenia	5/1,332	0.4	5/663	0.8
Grade 3 systemic reaction	75/1,332	5.6	28/663	4.2

n: number of subjects experiencing the endpoint listed in the first column M: number of subjects with available data for the relevant endpoint

Source: Adapted from STN 125682.0; Section 10, modified from Table 10.43, Table 10.47, Table 7.4, Table 7.6

Clinical Reviewer Comment: *The percentage of subjects with solicited adverse reactions was slightly higher in the Dengvaxia compared to the Placebo group. In general, the rates of solicited adverse reactions are within the range observed for preventive vaccines, except for headaches which are somewhat higher in both groups.*

Table 35 shows the solicited injection site reactions by dose in CYD14.

Table 35: Study CYD14, Solicited Injection Site Reactions Within 7 Days After Each Dose in the Reactogenicity Subset

Subjects experiencing at least one	Dengvaxia Group n/M	Dengvaxia Group %	Placebo Group n/M	Placebo Group %
Pain	--	--	--	--
Post-Dose 1	13/406	30.5	66/196	29.6
Post-Dose 2	13/303	23.0	65/135	20.5
Post-Dose 3	13/283	21.6	65/118	18.0
Erythema	--	--	--	--
Post-Dose 1	63/133	4.7	35/663	5.3
Post-Dose 2	43/131	3.3	20/658	3.0
Post-Dose 3	36/131	2.7	16/654	2.4
Swelling	--	--	--	--
Post-Dose 1	40/133	3.0	19/663	2.9
Post-Dose 2	25/131	1.9	7/658	1.1
Post-Dose 3	19/131	1.4	10/654	1.5

n: number of subjects experiencing the endpoint listed in the first 2 columns M: number of subjects with available data for the relevant endpoint

Source: Adapted from Original 125682; Clinical Study Report CYD14, Version 4, Section 10, modified from Table 10.51, Table 10.52, Table 10.53

Clinical Reviewer Comment: *Solicited injection site reactions were, in general, balanced between Dengvaxia and Placebo groups. The rates of solicited injection site reactions decreased with each successive dose.*

Table 36 shows the solicited systemic reactions within 14 days of each dose in CYD14.

Table 36: Study CYD14, Solicited Systemic Adverse Reactions Within 14 Days After Each Dose in the Reactogenicity Subset

Treatment Group	Dengvaxia Group n/M	Dengvaxia Group %	Placebo Group n/M	Placebo Group %
Fever	--	--	--	--
Post-dose 1	103/1,330	7.7	45/663	6.8
Post-dose 2	90/1,320	6.8	44/657	6.7
Post-dose 3	76/1,309	5.8	39/654	6.0
Headache	--	--	--	--
Post-dose 1	387/1,332	29.1	168/663	25.3
Post-dose 2	247/1,319	18.7	118/658	17.9
Post-dose 3	219/1,313	16.7	113/654	17.3
Malaise	--	--	--	--
Post-dose 1	312/1,332	23.4	148/663	22.3
Post-dose 2	192/1,319	14.6	100/658	15.2
Post-dose 3	183/1,313	13.9	104/654	15.9
Myalgia	--	--	--	--
Post-dose 1	255/1,332	19.1	124/663	18.7
Post-dose 2	174/1,319	13.2	92/658	14.0
Post-dose 3	156/1,313	11.9	76/654	11.6
Asthenia	--	--	--	--
Post-dose 1	229/1,332	17.2	97/663	14.6
Post-dose 2	158/1,319	12.0	74/658	11.2
Post-dose 3	142/1,313	10.8	73/654	11.2

n: number of subjects experiencing the endpoint listed, M: number of subjects with available data for the relevant endpoint

Source: Adapted from Original 125682; Clinical Study Report CYD14, Section 10, modified from Table 10.63, Table 10.64, Table 10.65

Clinical Reviewer Comment: *Solicited systemic adverse reactions were, in general, equally balanced between Dengvaxia and a Control groups.*

Table 37 shows the incidence and relative risk for hospitalized, severe, VCD cases by age group 2-8 years and 9-14 years during each time period in the study.

Table 37: Study CYD14, Incidence of Hospitalized Severe Virologically Confirmed Dengue[1] During the Trial Due to Any Dengue Serotype According to the Age Group (Age at Inclusion: 2 to 8 years, and 9 to 14 years) - Safety Analysis Set

Follow up period: Subjects Ages 2 to 8 Years at Vaccination	Dengvaxia Group Cases	Dengvaxia Group M	Placebo Group Cases	Placebo Group M	RR	(95% CI)
Year 1 (Day 0 to Dose 3)	5	3,533	4	1,767	0.625	(0.13; 3.15)
Year 2	5	3,508	5	1,754	0.500	(0.12; 2.17)
Active Phase	10	3,521	9	1,761	0.556	(0.20; 1.55)
Year 3	8	3,493	0	1,741	NC	(NC)
Year 4	9	3,479	4	1,737	1.123	(0.31; 4.99)
Year 5	9	3,440	6	1,718	0.749	(0.24; 2.56)
HP	20	7,575	7	3,790	1.430	(0.58; 4.00)
SEP	6	2,564	3	1,260	0.983	(0.21; 6.07)
HP/SEP	26	3,471	10	1,732	1.298	(0.61; 3.02)
Entire Study	36	3,491	19	1,743	0.946	(0.53; 1.75)
Follow up period: Subjects Ages 9 to 14 Years at Vaccination	**Dengvaxia Group Cases**	**Dengvaxia Group M**	**Placebo Group Cases**	**Placebo Group M**	**RR**	**(95% CI)**
Year 1 (Day 0 to Dose 3)	2	3,315	2	1,657	0.500	(0.04; 6.90)
Year 2	0	3,304	8	1,653	0.000	(0.00; 0.29)
Active Phase	2	3,310	10	1,655	0.100	(0.01; 0.47)
Year 3	3	3,285	1	1,646	1.503	(0.12; 78.91)
Year 4	4	3,276	2	1,639	1.001	(0.14; 11.06)
Year 5	4	3,218	2	1,608	0.999	(0.14; 11.05)
HP	8	7,071	3	3,543	1.336	(0.32; 7.82)
SEP	3	2,437	2	1,214	0.747	(0.09; 8.94)
HP/SEP	11	3,260	5	1,631	1.101	(0.35; 4.04)
Entire Study	13	3,280	15	1,641	0.434	(0.19; 0.98)

M: number of subjects present at the beginning of each year or mean of number of subjects followed during the years included in the considered period except for the HP and the SEP for which the denominator (M) will be the person-years followed in each of the 2 phases.

Source: Adapted from STN 125682.0; Interim Clinical

Study Report for CYD 14, Table 5.27

Clinical Reviewer Comment: *There was an increased RR for symptomatic, VCD cases in the Dengvaxia group, observed in subjects 2-8 years of age beginning in year 2 of the Hospital Phase and for the entire Hospital Phase/SEP. There was an increased RR for symptomatic, VCD case in the Dengvaxia group, observed in subjects 9-14 years of age in the first year of the Hospital Phase (HP) and the entire HP and the HP/SEP.*

6.2.12.3 Deaths

Active Phase: Four deaths occurred in the Dengvaxia Group following doseuries and were reported during the Active Phase. None were assessed as related to the vaccination by the Investigator. One subject in the control group who had been diagnosed with acute lymphoblastic leukemia died during Study Year 3.

HP/SEP: Six subjects (n=3 Dengvaxia Group [2 motor vehicle accidents, 1 myocarditis]; n=3 Placebo Group [encephalitis, sepsis due to pyelonephritis, ruptured aneurysm) died during the 3-year HP/SEP.

6.2.12.4 Nonfatal Serious Adverse Events

Two non-fatal SAEs reported for study CYD14 (one in the Dengvaxia group and one in the Placebo group) are described below:

Dengvaxia Group:
An 8-year-old male, 7 days post dose-1 had ADEM (Acute Demyelinating Encephalomyelitis). This illness was initially characterized by symptoms of lethargy and headache and then 2 days later by 4 episodes of right sided seizures associated with neck stiffness, alteration of the level of consciousness and left upper limb hemiparesis, leading to hospitalization. No fever or change to the subject's neurological examination was reported. Blood cultures were negative and elevation in acute phase reactants was not observed. The subject was initially managed as meningoencephalitis. Based on MRI results, the consulting pediatric neurologist suggested diagnosis of ADEM. Virological testing found negative Flavi-virus (FV) PCR in CSF and serum, negative herpes and enterovirus generic PCRs in CSF. Electroencephalography (EEG) showed intermittent slow awake background activity with no epileptic discharges. Acute neurotropic disease was ruled out: testing on serum, blood and urine and CSF revealed negative results for YF17D qRT-PCR and YF generic qRT-PCR detecting vaccinal virus replication and or wild-type YF strains. Generic PCRs for alpha- and FVs, enterovirus and herpesvirus performed on these samples provided negative results. The serological profile for dengue (ELISA IgM and IgG testing) was positive but this was not virologically confirmed since the results in the acute sample were negative for WT dengue virus (negative DS RT-PCR and negative NS1). Serological testing showed negative IgM for Epstein Barr virus, measles, rubella, and HIV; and showed positive IgM for Herpes Simplex I and II virus (HSV) and varicella zoster virus (linked to chickenpox that the subject had 2 months before the event). IgM for cytomegalovirus (CMV) was negative but IgG for CMV was positive. The acute sample was also negative for the PCR EV71.Throat swab for Influenza A/ H1N1 PCR was negative. In a stool sample neither enterovirus nor poliovirus were detected. Investigations on inborn error metabolism were negative. ANA (antinuclear antibodies by IF) were negative in serum. The Investigator updated the initial diagnosis to "Acute demyelinating encephalitis". The subject completely recovered 15 days after the onset of the event and was discharged. The subject did not present with any sequelae: the neurological examinations performed at day 51 and about

one month after his hospital's discharge were normal, and the MRI of the brain at day 135 reported no abnormal changes and no more hyperintense basal ganglion lesion.

Placebo Group:
In the Control Group, an 8-year old female child had angioedema with generalized urticaria 18 days after vaccination. The subject had no history of angioedema, asthma or atopic disorders, no allergy to food or drugs, no hypersensitivity reactions to vaccines or taking any drugs and insect bite. She had a family history of asthma (cousin but not her siblings or parents) but no history of allergic rhinitis or eczema and drug or food allergy. Eighteen days after dose, the child ate cooked prawns with no added additives at 8 pm and 4 hours later developed generalized swelling of face (predominantly lips and neck) with redness of face and generalized urticaria involving neck, back, arms and legs. She had no stridor, dyspnea, wheezing, giddiness or syncopal attack. It was reported that the subject had eaten seafood before but never had any allergic reaction. She was diagnosed with angioedema with generalized urticaria. Treatment included oral prednisolone and chlorpheniramine. The subject fully recovered 4 days after the first symptom. The subject was discontinued from following doses and was still followed for safety and dengue surveillance as per protocol. Medical assessment: The event of angioedema with generalized urticaria was reported by the Investigator as related to the control vaccine.

Clinical Reviewer comment: *The clinical reviewer agrees with the assessment of relatedness for deaths and SAEs.*

6.2.12.5 Adverse Events of Special Interest (AESI)

Unsolicited non-serious and serious hypersensitivity/allergic reactions occurring within 7 days after any dose were assessed in the reactogenicity analysis set and the safety analysis set, respectively.

No subject experienced a serious hypersensitivity/allergic reaction with 7 days of any dose.

Non-serious hypersensitivity/allergic reactions: Eight subjects (4 in the Dengvaxia Group and 4 in the Placebo Group) experienced at least one non-serious hypersensitivity/allergic reaction AESI within 7 days of any dose. These reactions were urticaria, rash and pruritus, and each resolved spontaneously in a short period of time.

The frequencies of AESIs were similar between the Dengvaxia and Placebo groups.

There were no cases of neurotropic or viscerotropic disease identified.

6.2.12.6 Clinical Test Results

No systematic assessment of biological laboratory parameters was performed in this study. In the context of dengue cases, clinical laboratory evaluation (hematocrit, platelet count, AST and ALT) was performed in subjects presenting acute febrile illness (i.e., temperature ≥ 38°C on at least 2 consecutive days) in both acute and convalescent specimens. The results of the clinical laboratory examinations in subjects who had dengue disease were consistent with the results normally observed in cases of acute dengue without evidence of DHF. The results of the clinical laboratory examinations for dengue with DHF were consistent with the WHO DHF severity

classification scheme, with grade 1 and grade 2 of DHF showing reductions in hematocrit and platelet counts and mild elevations of AST and ALT (data not shown).

6.2.13 Study Summary and Conclusions

Study CYD 14 was one of two Phase 3 trials conducted to support the safety and effectiveness of Dengvaxia vaccine to prevent dengue disease caused by dengue virus serotypes 1, 2, 3 and 4. The success criterion for the primary objective was met (VE 95%LBCI>25%) by the per protocol assessment of VE for the entire study, including ages 2 through 14 years and subjects, regardless of baseline dengue serostatus (estimated VE 56.5% [95%CI 43.8;66.4]).

In a post-hoc analysis, the estimated VE against symptomatic, VCD in subjects 9 through 14 years of age who were dengue seropositive at baseline was 79.2% (95% CI: 47.2; 97.7). Applicant requests an indication for Dengvaxia in persons 9 through 16 years who have laboratory confirmation of a previous dengue infection and who reside in a dengue endemic area, therefore this exploratory analysis of VE in 9 through 14 years in CYD14 subjects who were dengue seropositive at baseline provides support for this requested indication.

Vaccine efficacy by serotype varied, with higher efficacy shown for serotypes 3 and 4, although this study was not powered to assess VE by serotype and there were no pre-specified success criteria for serotype-specific VE. VE varied by dengue serostatus at baseline, with higher efficacy observed in subjects who were dengue seropositive at baseline, pre-vaccination #1, in post-hoc, exploratory analyses. Age-related differences in VE may be explained by dengue serostatus at baseline with younger age subjects less likely to be dengue seropositive at baseline compared to older age subjects. Vaccine immunogenicity and efficacy varied as a function of age with older children showing higher GMTs post-dose #3 and higher efficacy rates than younger children.

The vaccine had an acceptable safety profile for local and systemic adverse events, solicited and unsolicited up to 28 days post-dose; and SAEs (except for clinically severe, VCD cases) were balanced between Dengvaxia and placebo control groups for the full 60 months of the trial.

There was an imbalance in cases of severe dengue with more cases in the Dengvaxia group compared to the placebo group. This increased relative risk (RR) of severe dengue was greatest in the youngest age sub-group (2-5 years) and was observed beginning in the first year of the hospital phase. Although the increased RR for severe dengue was lower in age sub-groups 6-11 years and was observed more frequently in the second year of the hospital phase, it persisted in subjects through 14 years of age. Due to the relatively small percentage of subjects in the immunogenicity subset and the low numbers of cases of severe, VCD cases observed in the trial, there was an insufficient number of cases of severe dengue in which the dengue serostatus at baseline was known. Applicant undertook exploratory analyses using a case/cohort study design and using several methods to impute baseline dengue serostatus to clarify and explain this increased RR for severe dengue. (Please refer to section 9.2 for a description of these exploratory analyses.) Additionally, applicant pooled data from CYD 15, CYD 14 and CYD 23 to more clearly describe the increased RR for severe VCD cases (see section 8). The conclusion was reached that the increased RR for severe, VCD cases was primarily associated with a subject being dengue seronegative at baseline, although younger age, *per se*, could not be ruled out as contributing to this increased RR.
These data support the limitation of vaccine indication to persons 9 through 16 years of age, residing in dengue endemic regions and who are dengue seropositive at baseline. As part of the Pediatric Study Plan (see Section Executive Summary) the applicant will conduct further

analyses of data from subjects 2 through 8 years of age to clarify the relationship between age and dengue serostatus at baseline and efficacy and risk for severe/hospitalized dengue and will report those analyses as required by QTR-1, 2021.

6.3 Trial #3: CYD23

Title: Efficacy and Safety of Dengue Vaccine in Health Children Aged 4 to 11 years in Thailand (NCT 00842530)

Study start date: February, 2009 Study completion date: February, 2014

This was the first clinical endpoint efficacy trial conducted for Dengvaxia and was a Phase 2 study conducted in Thailand.

6.3.1 Objectives (Primary, Secondary, etc.)

Primary Objective
To assess the efficacy of dengue vaccine after three doses in preventing symptomatic VCD* dengue cases, regardless of the severity, due to any of the four serotypes in children aged 4 to 11 years.

Secondary Objectives
The secondary objectives for safety and immunogenicity in this study were the same as study CYD15. The reactogenicity subset included 1,050 randomly selected subjects. Of the 1,050 subjects in the reactogenicity subset, the immunogenicity subset included the first 300 subjects included at randomization.

6.3.2 Design Overview

The majority of the CYD23 study design elements were the same as for study CYD15 with respect to the following aspects:

- Vaccination schedule; control group received saline placebo
- Primary efficacy endpoint, case definition for virologically-confirmed dengue, management of suspected dengue cases, duration of efficacy follow-up in the Active Phase and follow up for severe/hospitalized dengue in the HP; re-consenting all willing subjects for the SEP during the fourth year of the study (which was the second year of the Hospital Phase) and resuming active surveillance for symptomatic VCD cases as well as continuation of active surveillance for severe/hospitalized dengue through second, third and fourth years of HP.(refer to Figure 1 for schematic diagram of the phases of the study)
- Secondary objectives and corresponding endpoints
- Randomization and blinding procedures
- Blood samples obtained for the immunogenicity subset and overall study population
- Safety evaluations
- Study success criterion; definitions of the statistical analysis sets; efficacy, safety (including reactogenicity) and immunogenicity analyses

Key differences in CYD23 and CYD15 study designs were:

- Study population: CYD23 enrolled subjects ages 4 through 11 years, whereas CYD15 enrolled subjects ages 9 through 16 years.
- Location: CYD23 enrolled subjects from the Asia-Pacific region (Thailand), whereas CYD15 enrolled subjects from Central America, South America, and Puerto Rico.

- Case Definition Symptomatic VCD case defined as an acute febrile illness with fever lasting for at least 1 day (temperature ≥37.5°C measured at least twice with an interval of at least 4 hours), and virologically confirmed by dengue RT-PCR or dengue NS1 ELISA Antigen test and occurring >28 days after the third dose. In CYD 15 the febrile episode needed to be a temperature ≥38.0C on at least two consecutive days.
- In CYD 23 the Hospital Phase is identified as CYD23/57 in the submission, however this reviewer has adapted the use of CYD23 to refer to the entire study from M0 to M60 for the sake of clarity.
- Surveillance monitoring for detection of febrile illness as first sign of a possible symptomatic dengue case differed in CYD23 compared to CYD15 and CYD14 in that school absenteeism was the starting point for surveillance in CYD 23. All absent students had their parents/guardians contacted by phone or text to ascertain whether the student had a febrile illness. Local outpatient clinic records were also screened for presentations with febrile illness and those parents/guardians contacted.

6.3.3 Population

The inclusion and exclusion criteria in this trial were the same as CYD 15, with the following exceptions:

- Inclusion criteria: The trial included children ages 4 to 11 years, attending one of the schools involved in the trial and living in the Ratchaburi Province.
- Exclusion criteria: Individuals were excluded if febrile illness (temperature ≥ 37.5°C) or moderate or severe acute illness/infection was present on the day of vaccination; personal or family history of thymic pathology (thymoma), thymectomy, or myasthenia; planned to attend another school (outside the trial area) or move to another city in the coming 30 months.

6.3.4 Study Treatments or Agents Mandated by the Protocol

Study agents were the same as for CYD15 and CYD14 except that in Cohort 1 the first fifty subjects in the control group had a rabies vaccine (Verorab) for first dose and saline placebo for second and third doses.

6.3.5 Directions for Use

Study agents were the same as for CYD15 and CYD14

6.3.7 Surveillance/Monitoring

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 identification of absenteeism during school-terms and phone calls/SMS or home visits during holidays (twice a week). Passive surveillance was also conducted in which parents were instructed to contact the study team for episodes of febrile illness.

Hospital Phase and SEP: monitoring was by passive surveillance of hospital records as per CYD 15.

Clinical Reviewer Comment:*. In the opinion of this reviewer the active case detection methods in CYD23 were comparable to CYD15 and CYD 14 and it was unlikely that cases of febrile*

illness during school days were missed. During vacation periods parents/guardians were contacted by phone or text exactly as in CYD 15.

6.3.8 Endpoints and Criteria for Study Success

Symptomatic VCD case defined as an acute febrile illness with fever lasting for at least 1 day (temperature ≥37.5°C measured at least twice with an interval of at least 4 hours), and virologically confirmed by dengue RT-PCR or dengue NS1 Ag ELISA and occurring >28 days after the third dose.

The pre-defined success criterion for efficacy for prevention of symptomatic VCD was an LB of the 95% CI of > 0. The PPAS was used for the primary analysis.

Clinical Reviewer Comment: *A dengue case required an acute febrile illness for at least one day* (temperature ≥*37.5°C measured at least twice with an interval of at least 4 hours), which was a less restrictive clinical threshold than that used in the two phase 3 trials (temperature ≥ 38.0°C for two consecutive days). This may have resulted in more cases of potential dengue infection being identified in this study, compared to studies CYD15 and CYD14. Virologic confirmation of a suspected dengue case was required in all three studies. Given that CYD23 is a supportive study and that CYD15 and CYD14 were adequately powered, the case definition of symptomatic VCD in study CYD23 is acceptable.*

6.3.9 Statistical Considerations & Statistical Analysis Plan

(Please refer to the statistical review for more comprehensive description of the SAP).

Sample size
A total of 4,002 subjects were planned to be enrolled: 2,668 subjects in the dengue group and 1,334 subjects in the control group. Assuming an alpha=2.5% (one-sided test), a yearly incidence of symptomatic VCD of 1.3%, an overall loss of follow-up of 15%, and a true efficacy of 70% after 3 doses, and expecting to get at least 27 cases, the study would have >80% power to show efficacy, defined as lower bound of the 95%CI >0.

Two statistical analyses were performed:

- A preliminary blinded safety analysis based on post-dose 1 and post-dose 2 was performed by an independent contract research organization
- A second analysis was performed to assess the efficacy after the complete schedule had been received (assessment of the primary objective), immunogenicity, and safety. It included all efficacy, immunogenicity, and safety data collected during the efficacy period (Active Phase) up to at least 13 months after the third dose of the last subject.

Analysis for the primary endpoints:
The following hypotheses were tested using an alpha of 2.5% H0: VE ≤ 0% H1: VE > 0% Where VE =100*(1-P_{VX}/P_{CO}) with P_{VX}: Density incidence (DI) in the Dengue group and with P_{CO}: DI in the Control group. DI was defined as the ratio of the number of cases occurring during the follow-up period to the population at risk. The statistical methodology was based on the use of the two-sided 95% CI of the VE. The CI was calculated using the Exact method described by Breslow & Day, 1987. VE in preventing symptomatic VCD would be demonstrated if the lower bound of the 95% CI was greater than 0. The PP analysis set was used for the main (primary) analysis.

The main efficacy parameters were described with 95% CI using the Exact method and the VE post-Dose 2 would be demonstrated as significant if the lower bound of the 95% CI was greater than 0.

The main immunogenicity parameters were described with 95% CI using the normal approximate method (GMT and Geometric Mean of the individual Titers Ratio) or the exact binomial distribution described using the Clopper Pearson method.

The main safety parameters were described with 95% CI using the exact binomial distribution described using the Clopper Pearson method.

Safety evaluation:
The subset of 700 subjects in the vaccine group gives a probability of 95% of observing an event with a true incidence of 0.43% (rule of three) (Hanley and Lippman-Hand, 1983).

Clinical Reviewer Comment: *CBER concurred with the SAP.*

6.3.10.1 Populations Enrolled/Analyzed
The populations analyzed for Study CYD23 were identical to Study CYD15 except for an analysis set in CYD 23 termed “Other Efficacy Analysis Set #1 and #2”. These analysis sets were designed to assess efficacy after at least one dose or at least after two doses, respectively. Please refer to section 6.1.10.1 of the clinical review.

6.3.10.1.1 Demographics
Table 38 shows the percentage of subjects by gender, age and race.

Table 38: Study CYD23, Subject Enrollment and Completion by Treatment Group

Treatment Group	Dengvaxia Group N = 2666 (%)	Placebo Group N = 1331 (%)	Total N = 3997 (%)
Male	1290 (48.4)	635 (47.7)	1925
Female	1376 (51.6)	696 (52.3)	2072
Age (years), Mean	8.16	8.20	8.17
Age (years), Min; Max	4.00; 12.0	4.00; 12.0	4.00; 12.0
Race: Asian	(100)	(100)	(100)

n: number of subjects experiencing the endpoint listed in the specified category.
Source: STN 125682.0; Clinical Study Report CYD23, Final version, Section 9, Table 9.26

Clinical Reviewer Comment: *Overall, there were slightly more female (51.8%) than male subjects (48.2%) and the mean age was 8.17 years. Subjects were well-balanced on gender, age and race.*

6.3.10.1.3 Subject Disposition

Table 39 shows subject enrollment, completion, and inclusion in analysis sets by treatment group.

Table 39: Study CYD23. Subject Enrollment, Completion, and Inclusion in Analysis Sets by Treatment Group

Treatment Group	Dengvaxia Group n (%)	Placebo Group n (%)	All Subjects n (%)
Enrolled and randomized subjects	2669 (100)	1333 (100)	4002 (100)
Subjects who completed Active Phase	2552 (95.6)	1276 (95.7)	3828 (95.7)
Discontinued subjects	117 (4.4)	57 (4.3)	174 (4.3)
Non-compliance with protocol	32 (1.2)	14 (1.1)	46 (1.1)
Lost to follow-up	6 (0.2)	8 (0.6)	14 (0.3)
Voluntary withdrawal not for AE	73 (2.7)	28 (2.0)	101 (2.5)
Full Analysis Set for Efficacy (FASE)	2557 (95.8)	1282 (96.2)	3839 (95.9)
Per-Protocol Analysis Set for Efficacy (PPSE)‡	2452 (91.9)	1221 (91.6)	3673 (91.8)
Safety Analysis Set (SAS)*	2666 (99.9)	1331 (99.9)	3997 (99.9)
Other Efficacy Analysis Set #1	2666 (99.9)	1331 (99.9)	3997 (99.9)
Other Efficacy Analysis Set #2	2584 (96.8)	1300 (97.5)	3884 (97.1)
Reactogenicity subset included in the SafAS*	697 (26.1)	350 (26.3)	1047 (26.2)
Full Analysis Set for Immunogenicity (FASI)‡	197 (7.4)	99 (7.4)	296 (7.4)

* Subjects were classified as per first vaccine received.
‡ Subjects were classified as per the treatment group to which they were randomized.
Source: STN 125682.0; Clinical Study Report CYD23, Final, Tables 4.2,4.3

Clinical Reviewer Comment: *There was a minimal level of protocol deviations in both groups and therefore the results of the study can be assumed to represent true differences between CYD vaccine and control groups on the primary and secondary endpoints.*

6.3.11 Efficacy Analyses

6.3.11.1 Analyses of Primary Endpoint(s)

The primary endpoint for CYD23 was VCD cases due to any serotype, assessed by the PPSE from 28 days post-dose. 3 (M13) to M25. Table 40 shows the observed VE during this assessment period.

Table 40: Study CYD23, Vaccine Efficacy Against Virologically Confirmed (VC) Dengue After 3 Doses of Dengvaxia, Subjects 4 through 11 years of Age – PPSE

Dengvaxia Group (N=2,452) Person-years at risk	Dengvaxia Group Cases	Placebo Group (N=1,221) Person-years at risk	Placebo Group Cases	VE %	(95% CI)
2,522	45	1,251	32	**30.2**	(-13.4; 56.6)

Cases: number of subjects with at least 1 VC dengue episode.

Occurrences: number of VC dengue episodes in the considered period. Source: Original 125682; Clinical Study Report CYD23, Final version, Table 5.1

Clinical Reviewer Comment: *The VE of the Dengvaxia vaccine was considered to have met the pre-specified efficacy success criteria if the lower bound of its 95% CI was greater than 0. After 3 doses of Dengvaxia vaccine, the overall VE estimate was 30.2% (95% CI: -13.4, 56.6). Therefore, the pre-specified criteria for success was not reached (the lower bound of its 95% CIs was not greater than 0). Serotype 2 was the predominant serotype of symptomatic, VCD cases in this study and that may have lowered the point estimate of VE given that in all three trials (CYD15, CDY14 and CYD23) VE for serotype 2 was generally lower than VE against dengue serotypes 1, 3 and 4.*

6.3.11.2 Analyses of Secondary Endpoints

Table 41 shows the incidence and Relative Risk of VCD cases during the active phase of CYD23.

Table 41: CYD23, Incidence and Relative Risk of Virologically-Confirmed Dengue Cases During the Active Phase According to Serotype, Subjects 4 Through 11 Years of Age - Other Efficacy Analysis Set #1

Virologically-confirmed dengue cases due to each serotype	Dengvaxia Cases	Placebo Cases	RR	(95% CI)
Serotype 1	14	18	**0.388**	(0.179, 0.826)
Serotype 2	52	27	**0.965**	(0.595, 1.60)
Serotype 3	4	11	**0.181**	(0.042, 0.612)
Serotype 4	1	5	**0.100**	(0.002, 0.894)
Not Identified*	5	1	2.51	(0.280, 118)

Other Efficacy Analysis Set #1: all subjects with at least one dose in the Active Phase

Cases: number of subjects with one virologically-confirmed dengue episode during the Active Phase.

* Virologically-confirmed dengue cases confirmed only by NS1 method were classified in the Not Identified category.

Source: STN 125682.0; Clinical Study Report CYD23, Final version, Section 9, Table 9.204.

Clinical Reviewer Comment: *Vaccine efficacy varied by serotype with serotypes 3 and 4 showing lower RR for symptomatic, VCD cases than serotypes 1 and 2. It is not clear as to why the Dengvaxia vaccine is more efficacious against serotypes 3 and 4 in this study. However, this pattern is consistent in all three clinical efficacy endpoint trials. The post-dose 3 GMTs do not clarify an association between titer and efficacy as in general in all three studies the serotype 2 GMTs were the highest post-dose 3 titers.*

Immunogenicity
Relationship between post-dose 3 antibody levels and symptomatic dengue cases is shown in Table 42 which shows the GMTs in cases and in non-cases in Study CYD23.

Table 42: Study CYD23, Dengue PRNT Assay GMTs at 28 Days After Dose 3, Subjects 4 through 11 Years of Age with Virologically-Confirmed Dengue Cases vs. Non-Cases, by Serotype - Full Analysis Set for Efficacy

--	Dengue cases (M)	Dengue cases GMT (95%CI)	Dengue Non-cases (M)	Dengu Non-cases GMT (95%CI)
Dengvaxia Group (N=2,557)	--	--	--	--
Serotype 1	9	55.6 (36.8; 83.9)	183	153.4 (114.3; 205.8)
Serotype 2	32	94.0 (73.4; 120.3)	183	350.3 (276.8; 443.5)
Serotype 3	1	154.0 (NC)	183	348.2 (286; 423.9)
Serotype 4	0	-	183	150.8 (127.5; 178.5)
Placebo Group (N=1,282)	--	--	--	--
Serotype 1	10	7.3 (3.1; 17.0)	90	24.9 (16.3; 37.8)
Serotype 2	19	24.9 (12.8; 48.4)	90	47.8 (28.8; 79.3)
Serotype 3	2	5.0 (NC)	90	41.4 (26.6; 64.3)
Serotype 4	4	50.5 (14.0; 182.1)	90	19.6 (13.4; 28.5)

N: number of subjects in the treatment group, M: number of subjects with available data for the relevant endpoint, NC: not calculatable.

Virologically-confirmed dengue: subjects with at least one virologically-confirmed dengue case 28 days after three doses during the Active Phase due to the considered serotype.

No virologically-confirmed dengue: subjects in the FASI who did not have virologically-confirmed dengue due to any serotype since V01.

Subjects with a virologically-confirmed dengue based on only an NS1 positive result were excluded. Source: STN 125682.0; Clinical Study Report CYD23, Final version, Table 5.4

Clinical Reviewer Comment: *Although there was no specific post-dose 3 GMT that was a reliable correlate of protection, there was a tendency towards efficacy with higher post-dose3 GMTs observed in this study, with non-cases having higher post-dose.3 GMTs compared to cases. This was a post-hoc exploratory analysis and is limited by the small number of cases observed.*

Dengue GMTs by Serotype
Immunogenicity was analyzed by the measurement of dengue neutralizing Abs using the plaque reduction neutralization test. All results are based on the FASI. Table 43 shows the GMT by serotype observed in CYD23.

Table 43: Study CYD23, GMT by Serotype, Pre-Dose 1, Post-Dose 3 and 1 Year After Dose 3, Subjects 4 through 11 Years of Age - FASI

Treatment Group	Dengvaxia Group (N=187-197) GMT (95% CI)	Placebo group (N=94-99) GMT (95% CI)
Serotype 1	--	--
Pre-Dose 1	42.8 (30.7; 59.6)	26.6 (17.6; 40.2)
Post-Dose 3	155 (116; 207)	27.8 (18.3; 42.2)
1-Year Follow-Up Post- Dose 3	120 (87.0; 166)	35.8 (23.1; 55.4)
Serotype 2	--	--
Pre-Dose 1	56.8 (40.3; 80.1)	43.7 (27.8; 68.7)
Post-Dose 3	358 (283; 453)	52.2 (32.3; 84.4)
1-Year Follow-Up Post- Dose 3	158 (117; 213)	46.1 (29.4; 72.4)
Serotype 3	--	--
Pre-Dose 1	31.5 (24.2; 41.0)	28.7 (19.3; 42.6)
Post-Dose 3	351 (289; 428)	46.2 (29.9; 71.4)
1-Year Follow-Up Post- Dose 3	125 (97.2; 161)	35.1 (23.0; 53.6)
Serotype 4	--	--
Pre-Dose 1	197 (21.7; 36.4)	23.2 (15.6; 34.6)
Post-Dose 3	188 (128; 178)	22.1 (15.3; 32.0)
1-Year Follow-Up Post-Dose 3	187 (120; 192)	45.9 (30.4; 69.3)

N: number of subjects with available data for the relevant endpoint.
Source: Adapted from Original 125682; Clinical Study Report CYD23, Final version, Table 5.10

Clinical Reviewer Comment: *CYD vaccination was immunogenic with a 3-7-fold increase from pre-dose.1 titer to post-dose.3 titer in the CYD vaccine group. GMTs decreased by 25-65% at the one-year follow-up time point for serotypes 1, 2 and 3.*

6.3.11.4 Dropouts and/or Discontinuations

Table 44 shows the protocol deviations during the Active Phase.

Table 44: Study CYD23, Subjects with Protocol Deviations During the Active Phase – Cohorts 1 & 2

Cohort	Dengvaxia Group n (%)	Control Group n (%)	All Subjects n (%)
Cohort 1	--	--	--
Other Efficacy Analysis Set #1	100 (100.0)	50 (100.0)	150 (100.0)
Other Efficacy Analysis Set #2	93 (93.0)	47 (94.0)	140 (93.3)
Full Analysis Set for Efficacy	92 (92.0)	47 (94.0)	139 (92.7)
Cohort 2	--	--	--
Other Efficacy Analysis Set #1	2,566 (100.0)	1,281 (100.0)	3,847 (100.0)
Other Efficacy Analysis Set #2	2,491 (97.1)	1,253 (97.8)	3,744 (97.3)
Full Analysis Set for Efficacy	2,465 (96.1)	1,235 (96.4)	3,700 (96.2)
Per-Protocol Analysis Set for Efficacy *	2,452 (95.6)	1,221 (95.3)	3,673 (95.5)
At least one deviation †	114 (4.4)	60 (4.7)	174 (4.5)
Did not meet all protocol-specified inclusion/exclusion criteria or definitive contraindications	19	13 (1.0)	32 (0.8)
Randomization error	0 (0.0)	2 (0.2)	2 (0.1)
Injection not performed	101 (3.9)	46 (3.6)	147 (3.8)
Code breaking by the Investigator	0 (0.0)	0 (0.0)	0 (0.0)
Delay between the injections not respected	15 (0.6)	13 (1.0)	28 (0.7)

The subjects of Cohort 1 received the second dose at month 9 instead of month 6. These subjects were therefore excluded from the PPSE.

†The number of subjects with at least one protocol deviation.

Source: STN 125682.0; Clinical Study Report CYD23, Final version, Section 9, Table 9.21

6.3.11.5 Exploratory and Post Hoc Analyses

The GMTs by serotype by dengue serostatus at baseline in CYD23 showed a similar pattern as was observed in trials CYD15 and CYD14, with substantially higher post-dose-3 GMTs in subjects who were dengue seropositive at baseline compared to subjects who were dengue seronegative at baseline (data not shown).

Exploratory, post-hoc analyses were performed on age sub-group 9 through 11 years of age because this age group is included in the requested Dengvaxia indication. None of these analyses were pre-specified and the statistical interpretations are limited by the smaller numbers of subjects and cases in this age sub-group. There were 6 cases out of 1033 person-years at risk versus 10 cases in 514 person-years at risk in the Dengvaxia and Placebo Groups, respectively (VE% 70.1 [95%CI 9.3, 91.1]). Although conclusions were limited by the small sample size and accordingly, low number of event, trends for serotype specific for VE in subjects 9 through 11 years of age were comparable to those observed in the full age cohort (2 through 11 years of age) with observation that serotype 2 predominated in both Dengvaxia (13/18 cases) and placebo groups (7/16 cases).

Clinical Reviewer Comment: *In this post-hoc, exploratory analysis, VE was 70.1 (9.3;91.1), however the numbers of cases are small with subjects, 9 through 11 years of age representing approximately 30% of the randomized subjects for the entire study. Exploratory analysis of VE by serotype there were more cases of symptomatic, VCD cases of serotype 2 than other serotypes. These results should be interpreted cautiously. Serotype 2 efficacy was lower than serotypes 1, 3 and 4 in CYD 15 and CYD 14, however efficacy against serotype 2 was observed to be even lower in Study CYD 23 compared to the two Phase 3 trials. The reason for this finding of quite low serotype 2 specific efficacy in CYD 23 is not clear. Post-dose 3 GMTs in dengue seropositive subjects at baseline were highest for serotype 2, suggesting that VE is a function of more than the magnitude of neutralizing antibodies induced by Dengvaxia vaccination. In theory, there may have been an antigenically variant serotype 2 strain circulating in Thailand during the active phase of this study, however there is no sequencing data available to support or refute such an explanation (26).*

6.3.12 Safety Analyses

6.3.12.2 Overview of Adverse Events

Table 45 shows a safety overview after any dose in CYD23.

Table 45: Study CYD23, Safety Overview After Any Dose by Treatment Group - Reactogenicity Subset - Safety Analysis Set

Subjects experiencing at least one:	Dengvaxia Group (N=697) n/M	Dengvaxia Group %	Placebo Group (N=350) n/M	Placebo Group %
Immediate unsolicited AE	0/697	0.0	0/350	0.0
Immediate unsolicited AR	0/697	0.0	0/350	0.0
Solicited reaction	578/697	83.5	281/35	80.3
Grade 3 solicited reaction	33/692	4.8	27/350	7.7
Solicited injection site reaction	426/695	61.6	218/34	62.5
Grade 3 injection site reaction	3/692	0.4	1/349	0.3
Solicited systemic reaction	538/695	77.7	261/35	74.6
Grade 3 systemic reaction	32/692	4.6	26/350	7.4
Unsolicited AE	317/695	45.5	162/35	46.3
Unsolicited AR	10/697	1.4	1/350	0.3
Unsolicited non-serious AE	308/697	44.2	154/35	44.0
Grade 3 unsolicited non-serious AE	21/697	3.0	14/350	4.0
Unsolicited non-serious AR	10/697	1.4	1/350	0.3
Grade 3 unsolicited non-serious AR	1/697	0.1	0/350	0.0
Unsolicited non-serious injection site AR	7/697	1.0	1/350	0.3
Unsolicited non-serious systemic AE	306/697	43.9	154/35	44.0
Unsolicited non-serious systemic AR	3/697	0.4	0/350	0.0
AE leading to study discontinuation *	0/697	0.0	0/350	0.0
SAE until 6 months after the last dose	90/697	12.9	44/350	12.6
SAE from 6 months after the last dose†	0/697	0.0	0/350	0.0
Death	0/697	0.0	0/350	0.0

n: number of subjects experiencing the endpoint listed in the specified category.
M: number of subjects with available data for the relevant endpoint.
* Identified in the termination form as SAE or other AE.
† SAEs collected up to the end of the Active Phase for the first analysis and all through the trial for the final analysis.
Source: Source: Original 125682; Clinical Study Report CYD23, Final version, Section 9, Table 9.37, and Table 9.77.

Clinical Reviewer Comment: *In general, there was a* ***proporti(onal*** *rate of adverse events between the Dengvaxia vaccine and the placebo control group. The higher rates of Grade 3 solicited reactions and Grade 3 systemic reactions in the control group compared to the Dengvaxia group were observed and are somewhat unusual in a preventive vaccine study but are not of a rate difference that would raise questions about the safety surveillance measures used in the study or the reporting of these adverse events. In Cohort 1, fifty subjects received the rabies vaccine and this may have contributed to a slightly higher percentage of certain adverse reactions in the control group compared to the Dengvaxia group.*

6.3.12.2.1 Local and Systemic Solicited Adverse Reactions

Table 46 shows the solicited injection site reactions within 7 days after each dose in the Safety Analysis Set.

Table 46: Study CYD 23, Solicited Injection site Reactions Within 7 Days After Each Dose - Reactogenicity Subset - Safety Analysis Set

Cohort	Reaction Evaluated After Specified Dose	Dengvaxia Group (N=697) n/M (%)	Control Group (N=350) n/M (%)
Cohort 1 Control: rabies vaccine	Injection site pain-after 1st dose	14/100 (14)	18/50 (36)
	Grade 3 Injection site pain-any dose	0/100 (0)	0/50 (0)
	Injection site erythema-after 1st dose	7/100 (7)	6/50 (12)
	Grade 3 injection site erythema-any dose	0/100 (0)	0/50 (0)
	Injection site swelling-after 1st dose	4/100 (4)	6/50 (12)
	Grade 3 injection site swelling-any dose	1/100 (1)	0/50 (0)
Cohort 2 Control: normal saline placebo	Injection site pain-after 1st dose	218/592 (37)	90/299 (30)
	Grade 3 Injection site pain-any dose	1/592 (0.2)	0/299 (0)
	Injection site erythema-after 1st dose	85/592 (14)	51/299/17)
	Grade 3 injection site erythema-any dose	0/592 (0)	0/299 (0)
	Injection site swelling-after 1st dose	58/592 (9.8)	26/299 (9)
	Grade 3 injection site swelling-any dose	1/592 (0.2)	1/299 (0.3)
Cohorts 1 & 2 Combined	Injection site pain-after 1st dose	232/692 (34)	108/349 (31)
	Grade 3 Injection site pain-any dose	1/692 (0.1)	0/349 (0)
	Injection site erythema-after 1st dose	92/692 (13)	57/349 (16)
	Grade 3 injection site erythema-any dose	0/692 (0)	0/349 (0)
	Injection site swelling-after 1st dose	62/692 (9)	32/349 (9)
	Grade 3 injection site swelling-any dose	2/692 (0.3)	1/349 (0.2)

N: number of subjects randomized to each treatment group, n: number of subjects experiencing the endpoint listed in the specified category, M: number of subjects with available data for the relevant endpoint.

Source: Adapted from Original 125682; Clinical Study Report CYD23, Final version Section 9, Tables 9.42, 9.43 and 9.44 and 9.45

Clinical Reviewer Comment: *Cohort 1 had a rabies vaccine as the control and showed higher rates for any injection site pain, erythema and swelling compared to Dengvaxia. Grade 3 injection site reactions were rare in both groups for both cohorts.*

Table 47 shows the solicited systemic reactions after the first dose in the Safety Analysis Set.

Table 47: CYD23, Solicited Systemic Reactions by Treatment Group After the First Dose - Reactogenicity Subset - Safety Analysis Set

Cohorts	Subjects experiencing at least one:	Dengvaxia (N=692) n/M (%)	Control (N=349) n/M (%)
Cohort 1 Control: rabies vaccine	Any Fever	12/100 (12)	8/50 (16)
	Grade 3 Fever	3/100 (3.0)	3/50 (6.0)
	Any Headache	28/100 (28)	18/50 (36)
	Grade 3 Headache	1/100 (1.0)	1/50 (2.0)
	Any Malaise	25/100 (25)	16/50 (32)
	Grade 3 Malaise	0/100 (0)	1/50 (2.0)
	Any Myalgia	15/100 (15)	11/50 (22)
	Grade 3 Myalgia	0/100 (0)	0/50 (0)
	Any Asthenia	15/100 (15)	12/50 (24)
	Grade 3 Asthenia	0/100 (0)	0.50 (0)
Cohort 2: Control: normal saline placebo	Any Fever	81/572(14.2)	42/289 (14.5)
	Grade 3 Fever	10/592 (1.7)	11/300 (3.7)
	Any Headache	246/592 (41.6)	105/299 (35.1)
	Grade 3 Headache	14/592 (2.4)	8/299 (2.7)
	Any Malaise	199/592(33.6)	87/299 (29.1)
	Grade 3 Malaise	11/592 (1.9)	7/299 (2.3)
	Any Myalgia	194/592(32.8)	76/299 (25.4)
	Grade 3 Myalgia	8/592 (1.4)	10/299 (3.3)
	Any Asthenia	160/592 (27)	70/299 (23.4)
	Grade 3 Asthenia	8/592 (1.4)	9/299 (3.0)
Cohorts 1 & 2 Combined	Any Fever	93/672(13.8)	50/339 (14.7)
	Grade 3 Fever	13/692 (1.9)	14/350 (4.0)
	Any Headache	274/692 (39.6)	123/349 (35.2)
	Grade 3 Headache	15/692 (2.2)	9/349 (2.6)
	Any Malaise	224/692(32.4)	103/349 (29.5)
	Grade 3 Malaise	11/692 (1.6)	8/349 (2.3)
	Any Myalgia	209/692 (30.2)	87/349 (24.9)
	Grade 3 Myalgia	8/692 (1.2)	10/349 (2.9)
	Any Asthenia	175/692 (25.3)	82/349 (23.5)
	Grade 3 Asthenia	8/692 (1.2)	9/349 (2.6)

n: number of subjects experiencing the endpoint listed in the specified category.

M: number of subjects with available data for the relevant endpoint.

Source: Adapted from Original 125682; Clinical Study Report CYD23, Final version, Tables 6.5, 9.57, 9.58 and 9.59.

Clinical Reviewer Comment: *The systemic solicited reactions were, in general, at rates to be expected for a preventive vaccine. Cohort 1 had a rabies vaccine as the control vaccine and had twice the rate of grade 3 fevers and headache compared to the Dengvaxia group. In Cohort 2 the control was normal saline and the higher rates of grade 3 reactions in this control group compared to the Dengvaxia group have no clear explanation. Combining the two cohorts there is an increased rate of grade 3 adverse reactions in the control as compared to the Dengvaxia group and this has no clear explanation.*

6.3.12.3 Deaths

Five deaths were reported, 4 occurred in the control group and 1 in the dengue group. None were considered related to treatment: the causes of death were drowning, road accidents, head injury, and T-cell lymphoma

6.3.12.4 Nonfatal Serious Adverse Events

One 11 year-old female subject experienced low-grade fever, headache and retro-orbital pain one day after the second CYD vaccination. She was admitted for supportive treatment and discharged one day later. This non-fatal SAE was attributed to vaccination by the clinical investigator.

6.3.12.5 Adverse Events of Special Interest (AESI)

Viscerotropic and neurotropic AEs were monitored, and none were identified in the six-month time following each vaccination.

6.3.13 Study Summary and Conclusions

CYD23 provided supportive immunogenicity, safety and efficacy data. Although this study failed to meet the success criteria on the primary endpoint of dengue cases due to any serotype, exploratory post-hoc analyses of efficacy in the age subgroup 9 through 11 years showed, in general, VE estimates that were more like trials CYD 15 and CYD 14 than did the PPSE analyses of the full age cohort of 4 through 11 years in this study CYD23. This trial showed similar patterns of responses on the GMTs post-dose 3 with dengue seropositive subjects at baseline having substantially higher immune responses by the $PRNT_{50}$ assay compared to the dengue seronegative at baseline. The safety data from this trial were consistent with the findings from the two Phase 3 trials supporting the conclusions that the vaccine was adequately safe and well- tolerated with respect to the endpoints of solicited local and systemic adverse events. No imbalance in SAEs were observed with the exception of clinically severe dengue cases which were higher in subjects' dengue seronegative at baseline than in placebo group.

6.4 Trial #4: CYD17

Title: CYD17: Lot-to-Lot Consistency and Bridging Study of a Tetravalent Dengue Vaccine in Healthy Adults in Australia (NCT 01134263)

Study start Date: October 5, 2010 Study completion date: February 2013

6.4.1 Overview of study design

CYD 17 was a Phase 3, lot-to-lot consistency study, conducted in Australia [a dengue non-endemic region] in healthy, 18-60-year-old adults. It was a randomized, placebo-controlled, observer-blinded, multi-center trial. Subjects were randomized to one of five groups (N=715):

- Group 1: N=164 subjects, Phase III lots of CYD vaccine, three doses at D0, M6, M12
- Group 2: N=163 subjects, Phase III lots of CYD vaccine, three doses at D0, M6, M12
- Group 3: N=163 subjects, Phase III lots of CYD vaccine, three doses at D0, M6, M12
- Group 4: N=168 subjects, Phase II lots of CYD vaccine, three doses at D0, M6, M12
- Group 5: N=57 subjects, normal saline placebo control, three doses at D0, M6, M12

All subjects were to receive 3 doses and provide a blood sample at baseline (pre-dose) for flavivirus (FV) status and immunogenicity assessment, and a blood sample 28 days after the third dose. Reactogenicity data were collected in all subjects after each dose for 7 days (local reactions) and 14 days (systemic reactions) after last dose of Dengvaxia.

CYD vaccine (Dengvaxia) dose: For both Phase II and Phase III lots of the CYD vaccine: 5 ± 1 log10 CCID50 of each live, attenuated, dengue serotype 1, 2, 3, 4 viruses. This trial was the first study to use Dengvaxia manufactured using the Phase III process.

Primary Objective: To demonstrate that three Phase III lots of Dengvaxia induce an equivalent immune response in terms of post-Dose 3 GMTs against the four parental serotypes.

Primary Endpoint: Dengue serotype-specific GMTs, measured in sera collected from all subjects 28 days after the third dose (PRNT50, dengue neutralization assay).

Success Criteria: The 95%CIs were calculated using the normal approximate method for GMTs. The statistical methodology was based on the use of the two-sided 95%CI of the differences of the means of the $\log_{10}$ transformed post- dose titers between pairs of lots. The CI for the differences was calculated using normal approximation of log-transformed titers. Equivalence among the three lots (comparisons of lot 1 to lot 2; lot 1 to lot 3, and lot 2 to lot 3) was demonstrated if, for each pair of lots and each serotype, the 95% CI was between >-0.301 and <0.301 (i.e., the three Phase III lots were considered equivalent if each of the pair-wise 2-sided 95% CIs comparisons of post-Dose 3 GMT ratios were between 0.5 and 2.0).

Secondary Objective, Immunogenicity: To demonstrate that data from one Phase II lot and pooled data from Phase III lots of Dengvaxia show an equivalent immune response in terms of post-Dose 3 GMTs against the four parental serotypes.

Secondary endpoint: Dengue serotype-specific GMTs, measured in sera collected from all subjects 28 days after the third dose (PRNT50, dengue neutralization assay).

Success criteria: If equivalence of the three Phase III lots was shown, the same equivalence testing approach used for the primary hypotheses was used to test if the Phase III investigational vaccine (pooled data from the three lots) was equivalent to the Phase II lot.

Safety objectives and endpoints: To describe the safety of Dengvaxia in all subjects after each dose. After each dose, safety evaluation included assessment of solicited local and systemic reactions (7days) and non-serious unexpected AEs (30 days), AESIs (including

hypersensitivity/allergic reactions [serious and non-serious; 7 days], serious viscerotropic and neurotropic disease [30 days]). SAEs were assessed from Day 0 through 6 months after the last dose;

6.4.2 Results

Subjects disposition
A total of 715 subjects were randomized: 164 subjects in the Phase III Lot 1 group, 163 subjects in the Phase III Lot 2 group, 163 subjects in the Phase III Lot 3 group, 168 subjects in the Phase II lot group and 57 subjects in the placebo group. Of a total of 712 vaccinated subjects, 712 (99.6%) were included in the Full Analysis Set (FAS) and 547 (75%) in the Per-Protocol Analysis (PPAS).

Of the enrolled subjects, 1.5% [11/712]) and 0.8% [6/712]) pre-maturely discontinued the study due to an AE and SAE, respectively. The number of subjects who did not complete the study due to an AE or an SAE was distributed evenly.

Clinical Reviewer Comment: *The four CYD lot groups were equally balanced in terms of the number of subjects who completed the study up to 28 days post third dose.*

Immunogenicity
Lot-to-lot differences and GMTs post-dose.3 results are shown in the following Tables 48 and 49.

Table 48. Study CYD17, Difference of Log_{10}GMT of Antibodies Against Parental Dengue Virus Serotypes Among Three Phase III Lots 28 Days After the Third Dose - Per Protocol Analysis Set

Serotype	Lot 1- Lot 2 Difference (95% CI)	Lot 2- lot 3 Difference (95% CI)	Lot 3-Lot 1 Difference (95% CI)
Serotype 1	0.055 (-0.067;0.178)	0.024 (-0.102;0.151)	-0.080 (-0.204;0.045)
Serotype 2	0.174 (0.009;0.340)	-0.120 (-0.297;0.056)	-0.054 (-0.225;0.117)
Serotype 3	0.058 (-0.068;0.184)	-0.042 (-0.167;0.082)	-0.016 (-0.144;0.113)
Serotype 4	0.144 (-0.006;0.295)	-0.060 (-0.207;0.088)	-0.085 (-0.242;0.073)

Lot consistency for each pair of lots was demonstrated if for each pair of lots and each serotype, the lower limit of the 95% CI was > -0.301 and the upper limit was < 0.301.

Source: STN 125682.0, CYD 17 Clinical Study Report, Final Version 4, Section 9, Table 9.103.

The lot consistency results, based on the FAS, were consistent with the results based on the PPAS.

Clinical Reviewer Comment: *The pre-specified criteria for lot to lot consistency were met for 11 of the 12 comparisons, with Lot 1-Lot 2, serotype 2, exceeding the upper limit of <0.301 by a small margin. There is unlikely to be any clinical significance to this one difference in serotype 2 Log-10 GMT antibody difference, and therefore, from a clinical perspective, lot to lot consistency was sufficiently demonstrated.*

Manufacturing Bridging
Since lot-to-lot consistency was not statistically demonstrated for all 12 comparisons, the hypothesis for manufacturing bridging could not be formally tested per original protocol design.

Table 49: Study CYD17, Comparison of GMT of Antibodies Against Parental Dengue Virus Serotypes in Pooled Phase 3 and Phase 2 Lots

Serotype	Pooled Phase 3 Lots N = 376 GMT (95%CI)	Phase 2 Lot N = 128 GMT (95%CI)	Phase 3 – Phase 2 Log_{10}GMT differences (95%CI)
Serotype 1	18.6 (16.5;20.9)	15.1 (12.4;18.4)	0.091 (-0.009;0.192)
Serotype 2	55.4 (47.2;65.1)	25.7 (20.6;32)	0.334 (0.202;0.46)
Serotype 3	70.2 (62.4;79.1)	83.6 (71.1;98.4)	-0.076 (-0.173;0.021)
Serotype 4	110.9 (96.1;127.9	115.4 (92.8;143.5)	-0.017 (-0.137;0.103)

M: Number of subjects available for the endpoint.

Equivalence between the pooled Phase III and Phase II was demonstrated if for each serotype, the lower limit of the 95%CI was > -0.301 and the upper limit was < 0.301.

Source: STN 125682.0, CYD 17 Clinical Study Report, Final, Section 9, Table 9.105.

Clinical Reviewer Comment: *The GMTs post dose-3 between the pooled phase 3 lots and the Phase 2 lot were similar. The differences between Phase 3 and Phase 2 lots met the pre-specified criteria of having a lower limit of the 95%CI > -.301 and the upper limit being <0.301, except for Serotype 2 where the upper limit was 0.466. In this reviewer's opinion and by these descriptive findings, the two lots of this CYD vaccine induced similar immune responses.*

Safety
No safety signals were identified, and the results were generally consistent with the data observed in the clinical endpoint efficacy studies, CYD15, CYD14, and CYD23 and will therefore not be discussed further.

Study Summary and Conclusions: Study CYD 17 adequately demonstrated lot to lot consistency between three Phase III lots of Dengvaxia in dengue seronegative adult subjects and demonstrated similar GMT responses in subjects immunized with Phase II lot of the vaccine. Dengvaxia had an acceptable safety profile in these subjects.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

The requested indication for Dengvaxia is the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in individuals 9 through 16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas.

Data from studies CYD 14, 15, and 23 were included in a pooled analysis of all evaluable subjects. These three studies included subjects from 2 years to 16 years of age, however the pooled analyses presented are primarily limited to subjects 9-16 years of age because these analyses are most relevant to the requested indication.

Moreover, an integrated analysis was performed to accomplish the following objectives:

- To improve the precision of the estimates for the following specific endpoints and analyses:
    - Vaccine efficacy (VE) for clinically severe virologically-confirmed dengue cases
    - VE for virologically-confirmed dengue cases that meets WHO criteria for dengue hemorrhagic fever (DHF)
    - VE for hospitalized virologically-confirmed dengue cases
    - VE by serotype
    - To assess the impact of age and dengue serostatus at baseline on the VE estimates

Integrated, pooled efficacy analyses of data from more than one study have limitations related to statistical interpretation of the results; possible variations in data collection in each study; serotype-specific dengue attack rates and changes in the proportion of subjects who are dengue seropositive at baseline; and variability in case definition and in virological confirmation of a dengue case. Therefore, these integrated analyses should be viewed as descriptive, although point estimates of efficacy and 95% CIs are given. The primary objective of presenting these integrated, pooled analyses is to provide a description of overall trends between the studies and to increase the numbers of analyzable cases of severe dengue for factors that occurred at a low frequency in individual studies.

In the context of VE, the two phase 3 efficacy studies (CYD 14 and CYD 15) were the same in terms of study design (clinical case definition and ascertainment, surveillance period, statistical success criteria and analysis populations), vaccination schedule, primary objectives and endpoints, and VE assumptions; the age of the enrolled population (CYD15: 9 through 16 years; CYD14; 2 through 14 years) and endemic regions (CYD15: South and Central America and Puerto Rico; CYD14: Asia-Pacific) differed. Study CYD 23 differed from the phase 3 studies in several aspects: the study was designed as a single center, phase 2 proof-of-concept study in 4 through 11 years in Thailand, to assess preliminary efficacy, and the clinical criteria used to define a dengue case was an acute febrile illness with fever lasting at least one day and a temperature of ≥37.5C measured at least twice with an interval of at least four hours. Virological confirmation was by reverse transcriptase polymerase chain reaction (RT-PCR) or dengue non-structural protein 1 (NS1) ELISA antigen test. In the two phase 3 studies the clinical definition of a dengue case required a temperature of ≥38.0C for at least two consecutive days and virological confirmation was by RT-PCR or NS1 ELISA antigen and confirmation of dengue serotype was by a Dengue Simplexa RT-PCR.

For these reasons, the presentation of integrated results will be articulated in presenting the individual estimates for Phase 3 studies CYD14 and CYD15 and the integrated estimate generated from a meta-analysis on CYD14/CYD15. As a sensitivity approach, the individual estimate for the supportive study CYD23 and the integrated estimate generated from a meta-analysis on CYD14 + CYD15 + CYD23 will be provided as supportive data on the Active Phase.

Clinical Reviewer Comment: *Integrated analyses of pooled data from more than one study can enhance the specificity of discrete findings if the studies were conducted in the same manner, such as with CYD 14 and CYD 15. The requirement for two consecutive days of fever in CYD14 and CYD 15, compared to one day of somewhat lower fever for CYD23 may have resulted in more cases of acute dengue being identified in CYD23 since the fever threshold was lower in degree and in persistence. Virological confirmation of a case of dengue differed between the three studies only in that confirmation of dengue serotype was by a Dengue Simplexa RT-PCR in CYD 14 and CYD 15 and was determined by repeating separate RT-PCR tests with different primers in CYD 23. Both methods for determining serotype should result in accurate characterization of serotype. CYD 23 was a smaller study conducted in a single country, and therefore the range of dengue serotype exposure was more limited than in the larger, multi-country phase 3 studies.*

Among the three studies, VE against dengue due to any serotype varied by age. Table 50 shows VE by age groups.

Table 50: Vaccine Efficacy by Age Group in Individual and Pooled Studies

Studies (Age Range)	Parameter	Dengvaxia Group	Placebo Group
CYD14 (2-14 years)	**Number of subjects**	6,709	3,350
--	**Number of cases**	117	133
--	**Vaccine Efficacy (95% CI) by PPSE**	**56.5** (43.8; 66.4)	--
CYD15 (9-16 years)	**Number of subjects**	12,573	6,261
--	**Number of cases**	176	221
--	**Vaccine Efficacy (95% CI) by PPSE**	**60.8** (52.0; 68.0)	--
CYD14 +CYD15 +CYD23 (9-16 years)	**Vaccine Efficacy (95% CI) mFASE**	**57.3** (50.7;63.0)	--

mFASE: Modified Full Analysis Set for Efficacy: all subjects who had three doses of Dengvaxia or placebo without major protocol deviations, VE 28 days post-dose 3 to month 25

PPSE: Per Protocol Set for Efficacy: all subjects who had three doses of Dengvaxia or placebo, per protocol; VE from 28 days post dose-3 to month 25

Source: Adapted from STN 125682.0; ISE, Tables 3.2.2.1, page 188; and Clinical Study Reports for CYD 14 (Table 5.1); CYD15 (Table 5.1) and CYD 23 (Table 5.1).

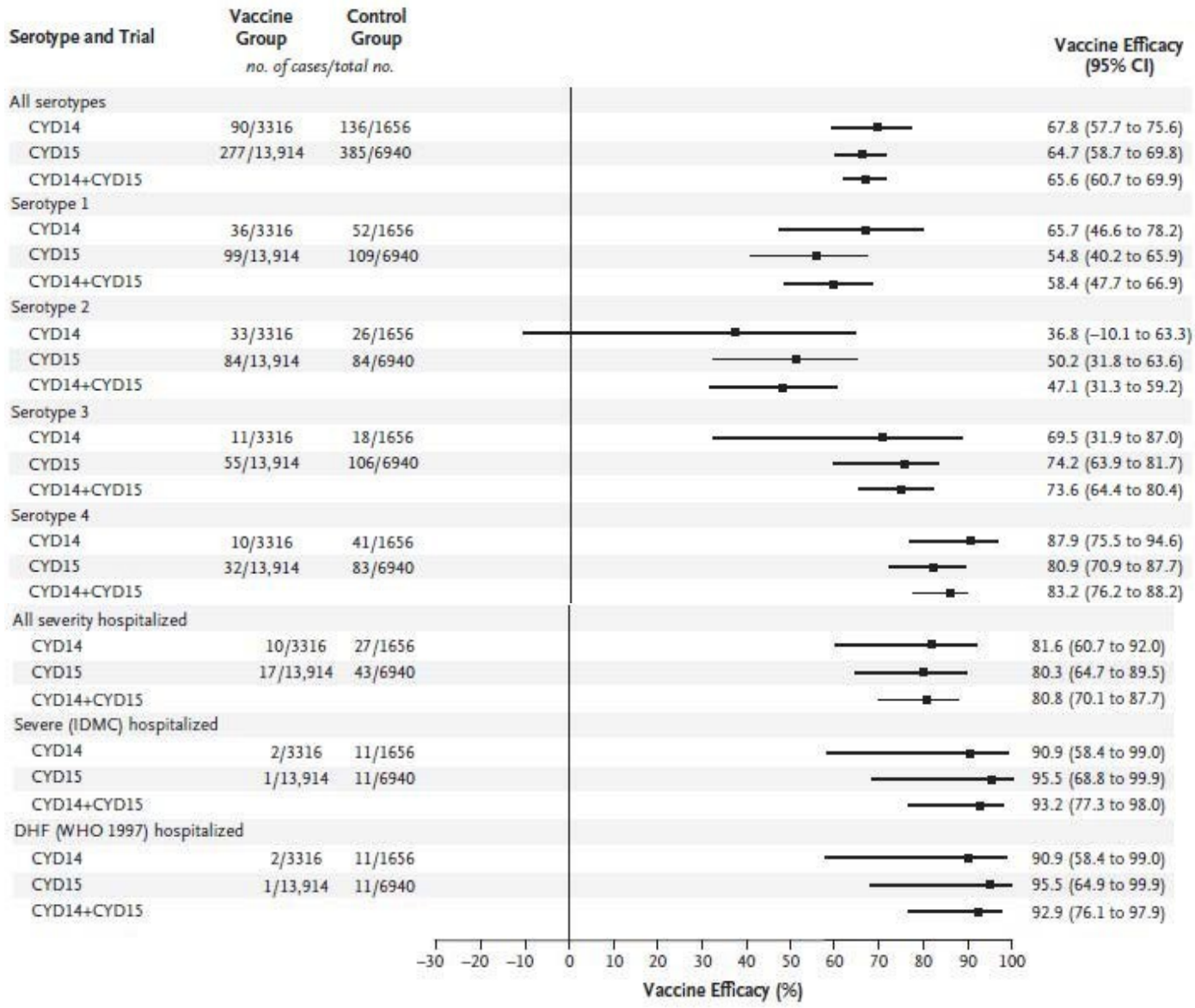
Clinical Reviewer Comment: *VE against symptomatic, VCD cases of any serotype was demonstrated in two Phase 3 studies, CYD14 and CYD15 by the pre-specified efficacy success criteria of LB of the 95%CI of >25%. The primary objective of the clinical endpoint efficacy trials*

was met; to demonstrate efficacy against symptomatic, VCD cases of any serotype in two major dengue endemic regions [South America for CYD 15 and the Asia Pacific for CYD14] which had different serotypes in circulation at different levels during the active surveillance period. These efficacy results include all randomized subjects, both dengue seropositive at pre-vaccination and dengue seronegative at pre-vaccination.

7.1.5 Analysis of Secondary Endpoint(s)

VE by serotype and by severity in individual trials CYD 14 and CYD 15 and in pooled analysis of CYD 14 and CYD 15 are shown in Figure 4.

Figure 4: Vaccine Efficacy Estimates by Serotype and Severity, in Subjects Aged 9 Through 16 Years During the Active Phase: Individual and Pooled Phase 3 Studies – Full Analysis Set for Efficacy



FASE: Full Analysis set for Efficacy: all subjects who received at least one dose of Dengvaxia or Placebo; VE from 28 days post-dose 3 to month 25

CYD (Chimeric Yellow Fever Dengue vaccine) Vaccine is Dengvaxia, identified as Vaccine Group; Control Group is normal saline Placebo Group Active Phase: from month 0 to month 25

Severe, hospitalized: subjects who met IDMC criteria for severe dengue and were hospitalized All-severity, hospitalized: subjects with dengue case of any severity and were hospitalized

DHF, hospitalized: subjects who met WHO 1997 criteria for DHF of any grade and were hospitalized

Source: STN 125682.0; Summary of Clinical Efficacy.pdf, Figure 10, page 69.

Clinical reviewer comment: *Vaccine efficacy against all dengue serotypes was 65.6% (60.7;69.9) in the pooled analysis of CYD 14 and CYD 15 by the FASE analysis set which included subjects 2-16 years of age who were either dengue seropositive or dengue seronegative at baseline. Efficacy against each serotype in the pooled analysis shows the same pattern of higher efficacy for serotypes 3 and 4 and lower efficacy for serotype 2, as shown in the individual trials. Efficacy against severe, hospitalized dengue and DHF (hospitalized) was quite substantial with point estimates of efficacy >90%; however, efficacy against severe dengue and against DHF was not a pre-specified endpoint and these findings should be considered to be observational and not supportive of an indication for Dengvaxia to prevent severe dengue or DHF. These pooled analyses of efficacy against any serotype, against each serotype and against severe dengue and DHF provide supportive evidence for the effectiveness of Dengvaxia in subjects 9 through 16 years of age, including subjects who were dengue seropositive and dengue seronegative at baseline, in prevention of dengue cases due to any serotype.*

Clinical Reviewer Comment: *Vaccine efficacy varies substantially as a function of dengue seropositive or dengue seronegative status at baseline. The limitation of indication to individuals who have laboratory confirmation of a prior dengue infection is because of the increased RR for severe dengue post-vaccination in subject's dengue seronegative at baseline (see Section 8 for pooled analyses of risk for severe dengue as a function of dengue serostatus at baseline). In the opinion of this reviewer, vaccine efficacy variance as a function of dengue serostatus at baseline would have been acceptable even though VE is much lower in subjects dengue seronegative at baseline, had there not been the safety risk of increased RR for severe dengue post-vaccination in the dengue seronegative subjects.*

7.1.7 Subpopulations

The potential influence of sex of the subject on vaccine efficacy was observed and VE was modestly numerically higher in males (approximately 8-10% compared to females).

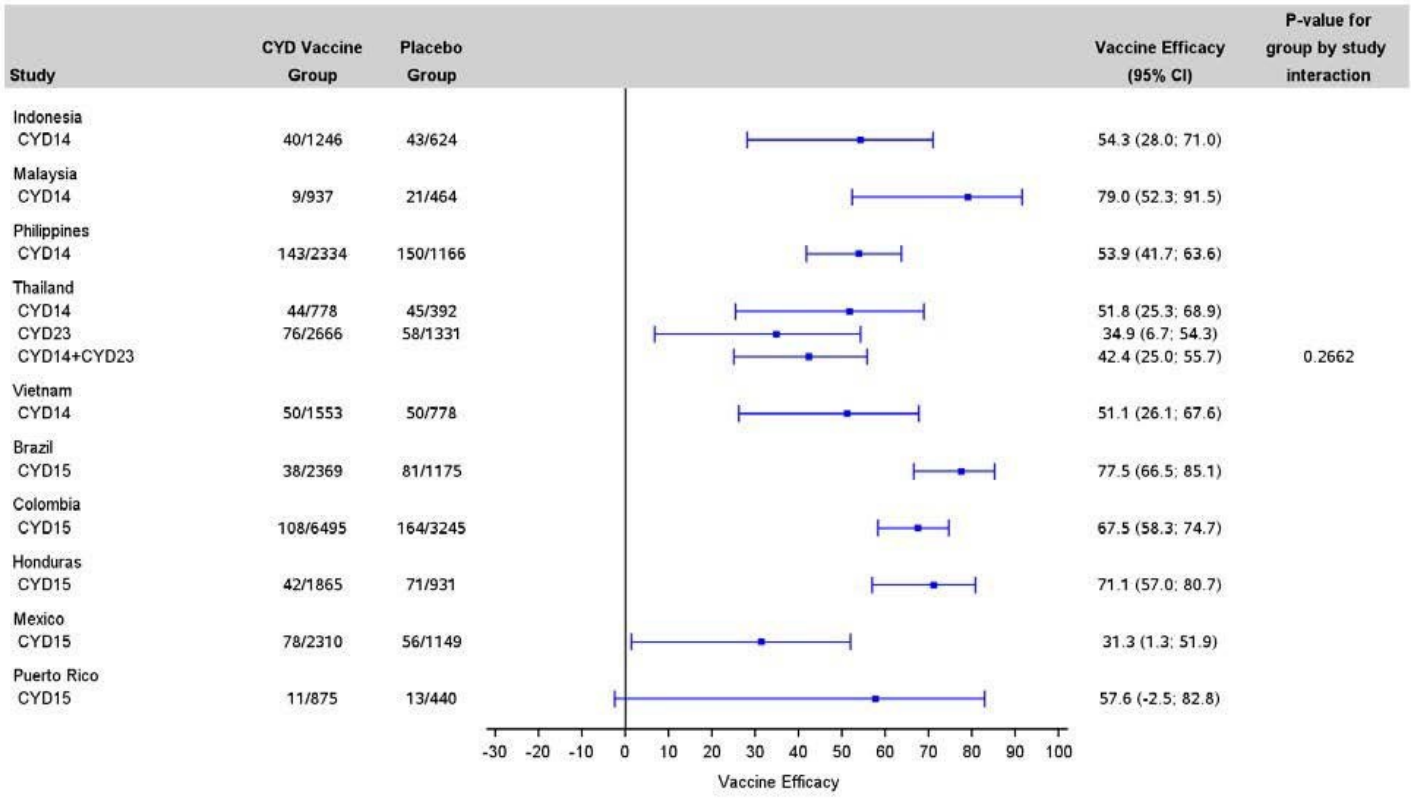
This is an observational finding with no clear biological explanation. Furthermore, the confidence intervals for pooled and individuals' studies were overlapping, and the p-values were non-significant (range 0.21- 0.84).

Clinical Reviewer Comment: *The vaccine efficacy in males was 8-10% higher compared to females. This is an observational finding with no clear biological explanation and the p-values are greater than 0.05 suggesting that the difference between males and females is not statistically significant. Of note, vaccine efficacy by BMI [not presented] shows that subjects with a "lean body mass" had mildly higher efficacy compared to subjects with an "average body mass" and that may be one part of the explanation for these differences, as the vaccine is*

administered by the subcutaneous (SC) route and females may have had somewhat more subcutaneous fat compared to the males.

Vaccine efficacy varied by country in the three clinical efficacy endpoint studies as shown in Figure 5.

Figure 5: VE Against Symptomatic Virologically-Confirmed Dengue Cases Post-Dose 3 Due to Any of the 4 Serotypes by Country – mFASE



The numerator is the number of subjects with a symptomatic VCD episodes in the considered period. The denominator is the number of subjects enrolled in the SEP period. Integrated Vaccine Efficacy and CIs are calculated using Cox regression model.

Vaccine Efficacy of a study is calculated using Density incidence: cases per 100 person-years at risk.

mFASE: Modified Full Analysis Set for Efficacy: includes all subjects who received three doses of vaccine or placebo without major protocol deviations

Subject Ages: subjects in CYD14 were 2-14 years of age and subjects in CYD 15 were 9-16 years of age Source: STN 125682.0; Summary of Clinical Efficacy, pdf., Figure 20, page 178

Clinical Reviewer Comment: *VE varied substantially by country. Country-specific VE was not a pre- specified endpoint and the studies were not powered to assess this endpoint, therefore these data should be assessed with this limitation considered. Several factors contributed to this variation. The percentage of subjects who were dengue seropositive at baseline varied between 56%-93%, by country, with Puerto Rico having 56% dengue seropositive at baseline and Colombia having 88% dengue seropositive at baseline, and the dominant serotype in circulation*

during the study varied by country. Countries with higher percentage of subjects that were dengue seropositive at baseline and where serotypes 3 and 4 predominated had higher overall vaccine efficacy rates. It is likely that country-specific VE rates may vary year to year as a function of the predominant dengue serotypes in circulation during any given year.

Serotype-specific, VCD cases by country in control groups were analyzed.

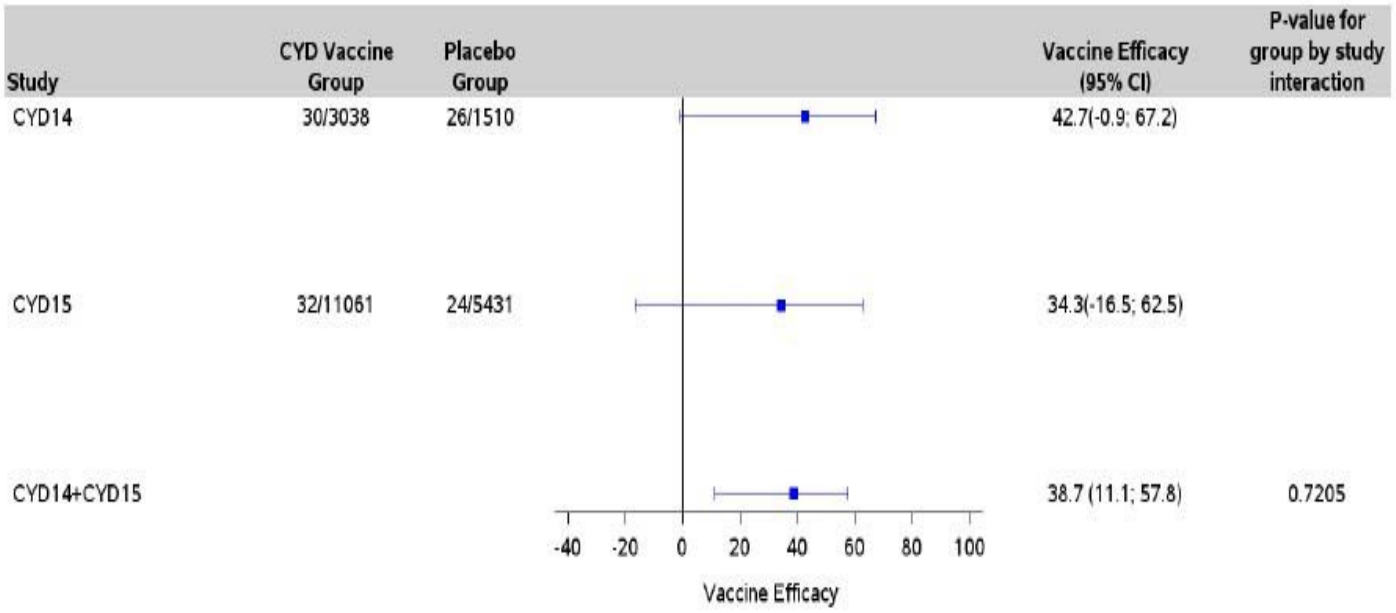
In CYD14 conducted in the Asia-Pacific region serotype 1 was predominant with 126 of 323 total cases in control group (39%); serotypes 3 and 4 represented 23% and 22% of dengue cases, respectively; and serotype 3 represented 13% of dengue cases. However, within the individual countries dengue cases by serotype varied with the Philippines having a predominance of serotype 1 cases and Vietnam having a predominance of serotype 4 cases. In CYD15 conducted in South and Central America and Puerto Rico, there was a more balanced range of serotypes, overall, with 109 of 396 dengue cases (27%) serotype 1 and serotypes 2, 3 and 4 were 21%, 27% and 21% respectively. However, Brazil had a predominance of serotype 4 and Puerto Rico had a predominance of serotype 1. VE varied by serotype in CYD14 and CYD15, with generally higher efficacy for serotypes 3 and 4 and lowest efficacy for serotype 2. Serotype-specific attack rates by country vary from year to year and given the variability in vaccine efficacy by serotype it is likely that country specific efficacy will vary from year to year. Country-specific efficacy rates were not a pre-specified endpoint and the studies were not powered to assess this endpoint. Two different dengue-endemic regions of the world were chosen for CYD15 and CYD14 to capture a diverse range of serotypes during the Active Phase, however it was not considered feasible to pre-specify serotype-specific efficacy endpoints for these studies due to the unpredictable nature of annual dengue attack rates by serotype. Assessments of serotype-specific efficacy and country-specific efficacy are limited by these studies being powered on the endpoint of efficacy against virologically-confirmed dengue cases of any serotype.

7.1.8 Persistence of Efficacy

The persistence of VE in the prevention of dengue cases due to any serotype was evaluated during the SEP which started during year two of the Hospital Phase (year four of the trial), for CYD 14 and CYD 15; approximately 48 months after dose 3. Subjects were re-consented before entering the SEP phase and approximately 92% of all subjects in Studies CYD 14 and 15 agreed to participate in the SEP phase, during which both active case detection for any dengue case was resumed as well as continued assessment of any case of severe/hospitalized dengue.

The complete study reports for the SEP phase in CYD 14 and CYD 15 are anticipated to be submitted at a later date. The VE data available, shown in Figure 6, is based on the SEP period in 9 through 16-year-old subjects collected over a 14-15-month time period, from approximately M45 to M60.

Figure 6: VE Against Symptomatic Virologically-Confirmed Dengue Cases During the SEP



The numerator is the number of subjects with a symptomatic VCD episodes in the considered period. The denominator is the number of subjects enrolled in the SEP period. Integrated Vaccine Efficacy and CIs are calculated using Cox regression model.

Vaccine Efficacy of a study is calculated using Density incidence: cases per 100 person-years at risk.

FASSEP: Full Analysis Set for the Surveillance Expansion Period; all subjects who consented to continue enrollment for the SEP period Source: STN 125682.0, ISE, Figure 3.4.6.1, page 1198 of pdf.

Clinical Reviewer Comment: *VE against symptomatic, VCD cases in 9-16 years declines during the first 14-15 months of the SEP period, which is from M45 to M60 of the study, compared to the VE observed in the Active Phase of CYD14 and CYD15 from month 13 to month 25 {VE in CYD14 was 56.5% (43.8;66.4); VE in CYD15 was 60.8% (52.0;68.0)}. Numerous factors may influence this finding such as decline in neutralizing antibodies and changes in the serotype specific dengue in circulation during this time, compared to the Active Phase. These data are incomplete and the final twelve months of data from the last part of the SEP period are to be submitted at a later date. The applicant plans to conduct two studies to evaluate the safety and efficacy of a booster dose of Dengvaxia. Waning vaccine efficacy is a potentially significant, if preliminary, observation, which suggests that additional data may help inform whether a boosting dose (s) of this vaccine might be needed to maintain efficacy.*

7.1.11 Efficacy Conclusions

The following summary statements concerning efficacy of Dengvaxia are based upon data presented in Section 7 and in Sections 6.1, 6.2 and 6.3.

1. VE against VCD cases due to any serotype met the pre-specified success criterion of the LB of the 95%CI>25% in CYD 15 and CYD14; with VE of 60.8% (52.0,68.0) by PPSE in 9-

16 years in CYD15; and VE of 56.5% (43.8.66.4) by PPSE in 2-14 years in CYD 14 and VE of 69.4% (52.2,80.6) by mFASE in 9-14 years in CYD14. The estimate of efficacy varied by serotype in a consistent manner across all three studies, with generally higher efficacy against serotypes 3 and 4 compared to serotypes 1 and 2; however, this result was a secondary objective and the studies were not powered to assess serotype-specific efficacy.

2. There are supportive data from secondary endpoints that the vaccine reduces the rate of clinically severe dengue during the Active Phase, from M0 to M25: {80.8% (42.7,94.7) in CYD14; 91.7% (31.4,99.8) in CYD15} and DHF {80.0% (52.7,92.4) in 9-14 years in CYD14; 95.0% (64.9,99.9) in 9-16 years in CYD15} observed in both Phase 3 studies individually and in the pooled analyses. However, data on severe dengue cases from M0 to M60 show a lesser effect of Dengvaxia on preventing severe dengue and data from M61 to M72 have not yet been submitted. The efficacy trials were not powered to assess an endpoint of prevention of severe dengue and these data do not support such an indication and should be viewed as descriptive observations.
3. Neutralizing Ab titers alone cannot fully explain the observed VE. Other possible factors contributing to the probability of the dengue diseases to occur include the age, and most importantly, the dengue serostatus of the subject at baseline.
4. Dengue serostatus at baseline, pre-vaccination, is a strong predictor of $PRNT_{50}$ Ab at titers 28 days post-dose 3, and there was a tendency of higher vaccine efficacy against any dengue case with higher post-dose 3 GMTs.
5. Age-specific differences were noted with higher efficacy associated with increasing age. However, age is primarily a surrogate marker for likelihood of a prior dengue infection at baseline. At this time, the effect of age on efficacy is not clearly understood, primarily due to the limitations of the immunogenicity subset, and shall be explored in further analyses to be conducted by the applicant as part of the PMR for their PSP and the deferral for ages 2-8 years.
6. VE varied by country and is related to the percentage of subjects who are dengue seropositive pre-vaccination and to the serotype-specific dengue attack rates during a given time period.
7. Preliminary data from the SEP period shows that vaccine efficacy is waning over time by months 45 to 60 in CYD14 and CYD15 which is 33-48 months after completion of the three dose vaccination series.

Clinical Reviewer Comment: *The data from the three clinical efficacy endpoint studies (CYD15, CYD14 and CYD23) support the requested indication for prevention of dengue cases of any serotype in ages 9 through 16 years in subjects living in dengue endemic regions, and who have laboratory confirmation of a prior dengue infection at baseline.*

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

The pooled analysis of safety included seventeen studies. In each study, Dengvaxia (0.5mL) was administered at D0, M6 and M12.

The safety evaluation included assessment of solicited local and systemic adverse reactions, Unsolicited adverse reactions; SAEs and AESIs. The Safety Analysis Population included subjects who had received at least one dose of Dengvaxia vaccine or normal saline placebo or comparator vaccine. All safety analyses were descriptive.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

The following studies were included in the pooled analyses for safety and were considered the "main" safety studies by the applicant: Children (≥2 years), adolescents, and adults: CYD12 (Group 1), CYD13, CYD14, CYD15, CYD17, CYD22, CYD23/CYD57, CYD24, CYD28, CYD30, CYD32, CYD47, and CYD51 (Group 1); Infants and toddlers (i.e., from 9 months to < 2 years): CYD08, CYD29, and CYD33.

A total of 19,120 subjects ages 9-17 years received at least one dose of Dengvaxia per the final schedule and 9,498 subjects ages 9-17 years received at least one dose of normal saline placebo. The safety population included subjects for whom the following data were available: for whom 28 day solicited local reactions; solicited systemic adverse events and unsolicited systemic adverse events; SAEs and AESIs; were available was 3,180 Dengvaxia recipients and 1,478 normal saline placebo recipients, ages 9-17 years.

Clinical Reviewer Comment: *Pooled safety analyses can provide a more comprehensive overview of safety findings and may, if they constitute a significantly larger number of evaluable subjects, identify rare adverse events. The safety population from the three clinical endpoint studies (CYD 15, CYD 14, and CYD 23/57) comprised >90% of the total evaluable subjects. The Integrated Overview of Safety that is most relevant, clinically, is the increased sensitivity of the analysis of the increased relative risk for severe dengue as a function of dengue serostatus at baseline. Additionally, the Integrated Overview of all severe allergic Adverse Events; all related SAEs; all viscerotropic or neurotropic AEs; and any AESI that occurs with a larger number of subjects in the pooled analysis provide a more comprehensive view of these rare events.*

8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials

The safety evaluation, monitoring and methods for data collection were the same in all studies. Reactogenicity was assessed in a subset of subjects (10-20% of the study population, depending on the study). Severity rating scales were the same in each study. Safety findings are descriptive therefore there are no statistical caveats that would confound these findings. Less than 1% of the total number of subjects received a comparator vaccine, and those subjects' data were not included in any comparative assessment of safety.

8.4 Safety Results

8.4.1 Deaths

There were no deaths attributable to Dengvaxia in any of the three clinical efficacy endpoint studies, CYD15, CYD14 and CYD23, and there were no deaths attributable to Dengvaxia in any of the studies conducted by the applicant which contributed to the safety data base.

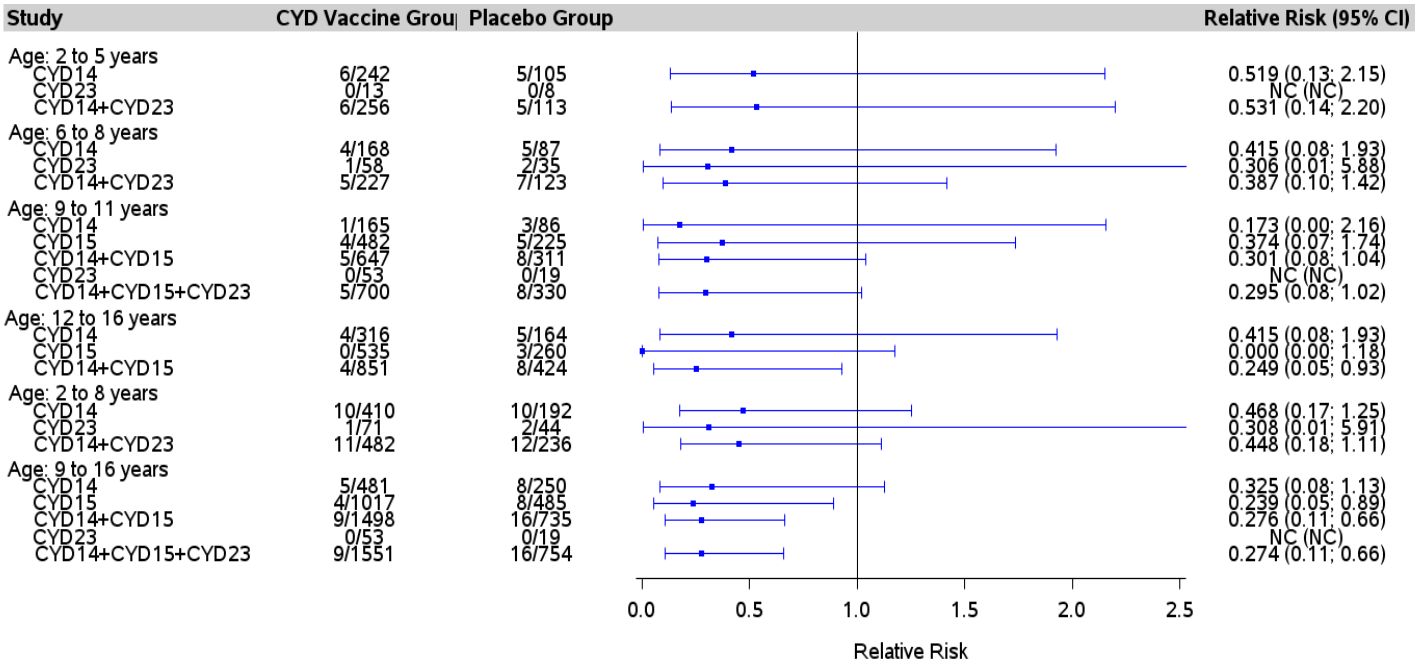
8.4.2 Nonfatal Serious Adverse Events

The overall frequency and nature of non-fatal SAEs (excluding clinically severe dengue) reported within 28 days or within 28 days and 6 months from any dose were similar between the Dengvaxia and Control groups, and mostly corresponded to common medical conditions

expected in each age group. In the Dengvaxia group, 0.8% of adults and 0.6% of subjects 9 through 16 years reported at least one SAE within 28 days after any dose, and 2.8% of both adults and subjects 9 through16 years reported at least one SAE from 28 days to 6 months after any dose. There were 4 related SAEs observed up to 28 days after any dose in the Dengue Group, all of which occurred in subjects ages 9 through 16 years of age (urticaria, asthma, acute polyneuropathy and tension headache) and are discussed along with other reported SAEs in the context of the review of the individual studies in which they occurred, i.e., Sections 6.1.12, 6.2.12, and 6.3.12

Cases of severe/hospitalized dengue were considered as SAEs in all three studies. The forest plots in Figures 7 and 8 show that there was an increased relative risk for severe/hospitalized dengue in subjects as a function of their age and their dengue serostatus at baseline during the entire study period from M0 to M60 or M72.

Figure 7: Relative Risk for Hospitalized Virologically-Confirmed Dengue Cases Due to Any Serotype During the Entire Study by Age Group – Subjects Dengue Seropositive at Baseline – Efficacy Studies Integrated/Pooled

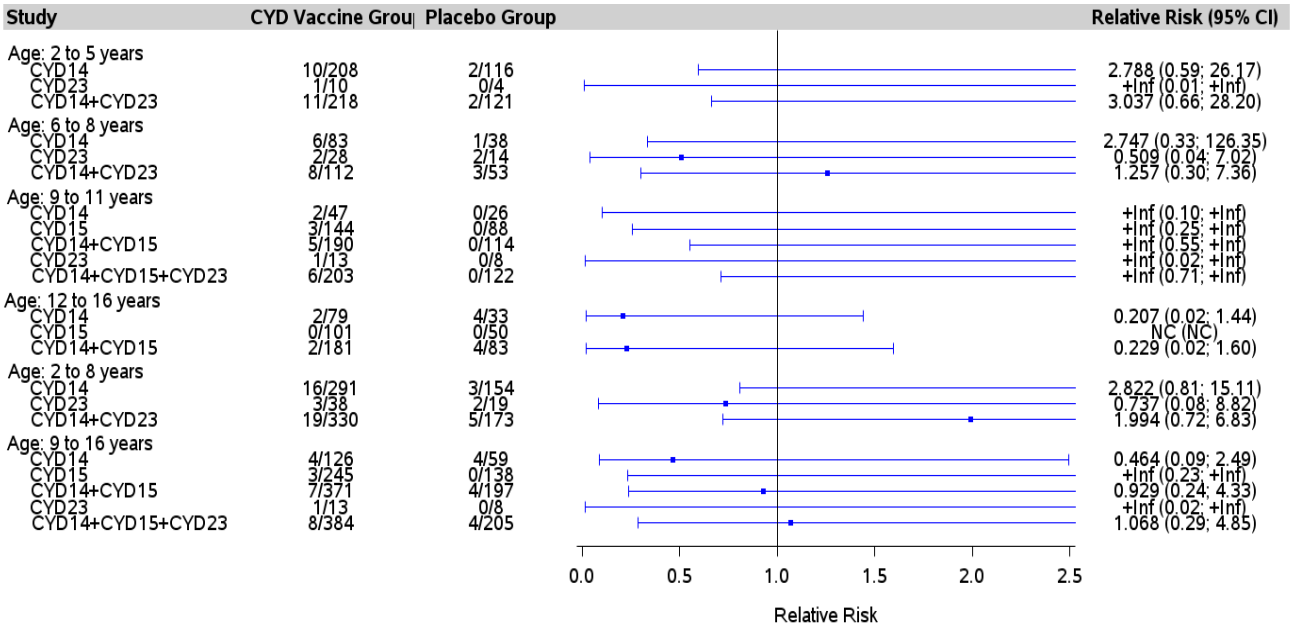


CYD14 and CYD15 data are up Year 3 Hospital Phase; SEP, CYD23 data are up to Year 4 Hospital Phase Pooled Analysis CYD14+CYD15+CYD23 are up to Year 3 Hospital Phase

During the entire study: from month 0 to Year 3 or Year 4 of Hospital Phase

Dengue seropositive: Dengue seropositive subjects are those with titers ≥ 10 (1/dilution) against at least one dengue serotype at baseline. Source: STN 125682.0, ISS pdf. Figure 3.34.2, page 5955.

Figure 8: Relative Risk for Hospitalized Virologically-Confirmed Dengue Cases Due to Any Serotype During the Entire Study by Age Group – Subjects Dengue Seronegative at Baseline – Efficacy Studies Integrated/Pooled



CYD14 and CYD15 date are up Year 3 Hospital Phase; SEP, CYD23 data are up to Year 4 Hospital Phase Pooled Analysis CYD14+CYD15+CYD23 are up to Year 3 Hospital Phase

During the entire study: from month 0 to Year 3 or Year 4 of Hospital Phase

Dengue seronegative: Dengue seronegative subjects are those with titers <10 (1/dilution) for all four serotypes Source: STN 125682.0, ISS pdf. Figure 3.34.1, page 5954.

Clinical Reviewer Comment: *There was an increased RR (Figure 8) for severe/hospitalized dengue in subjects who were dengue seronegative at baseline and who were age 2-5 years or age 6-8 years (analysis of individual study CYD14, pooled analysis of CYD14 and CYD23). Although this increased relative risk was lower in subjects ages 9-16 years, it still exceeded 1.0 RR for the pooled analysis of all three studies (RR 1.068; 0.29,4.85 for pooled analysis of CYD14, CYD15 and CYD23). Conversely, there was a decreased relative risk (Figure 7) for severe/hospitalized dengue in subjects who were dengue seropositive at baseline in all age subgroups in analysis by individual study and by pooled study analyses. These findings support the limitation of indicated use of Dengvaxia to individuals who have laboratory confirmation of a prior dengue infection.This observation of an increased RR for severe dengue post-vaccination in subjects who were dengue seronegative at baseline is a major finding from the clinical efficacy endpoint studies and affected the requested indication for Dengvaxia by limiting vaccination to individuals with laboratory confirmation of a prior dengue infection. The requirement for either medical record documentation of laboratory-confirmed prior dengue infection or serological testing pre-vaccination in individuals with no medical history of a prior dengue infection should be considered prior to the administration of Dengvaxia. Health Care Providers will need to be aware of this limitation of indication to avoid vaccinating dengue seronegative individuals and serological confirmation of dengue serostatus will require blood*

testing and waiting for serological test results until a rapid diagnostic, point of care, test is available.

The increased RR for severe dengue post-vaccination in subjects from all three clinical endpoint efficacy studies (CYD15, CYD14 and CYD23) from the time point of 28 days post-dose 3 (M13) until approximately M66, is shown in Table 51, by previous dengue infection status at M13 assessed by the anti-NS1 Ag ELISA. All subjects had post-dose 3 sera drawn, per protocol.

Table 51: Number of Events and Incidence of Severe Dengue* From Month 13 to approximately Month 66 in Children 9 through 16 Years of Age, by Previous Dengue Infection Status, in Studies CYD15, CYD14 and CYD23

Dengue Infection Status at Month 13[†]	**Dengvaxia n (Incidence[‡], %)**	**Placebo n (Incidence[‡], %)**	**Hazard Ratio of Severe Dengue (95% CI)**
Previous Dengue Infection (Dengue seropositive at Month 13)	10 (0.068)	27 (0.401)	**0.18** (0.09; 0.37)
No Previous Dengue Infection (Dengue seronegative at Month13)	12 (0.380)	1 (0.069)	**6.25** (0.81; 48.32)

n: number of subjects with severe dengue cases
CI: confidence interval
Study 1, NCT01374516; Study 2, NCT01373281; Study 3, NCT00842530; Study 4, NCT01983553

[*] Severe Dengue according to IDMC (Independent Data Monitoring Committee) definition: Proven dengue fever (2 days fever + virological confirmation) plus one of the following: (a) Platelet count ≤ 100,000/μL and bleeding plus plasma leakage (effusion on chest x-ray [CXR] or clinically apparent ascites including imaging procedures or hematocrit ≥ 20% above baseline recovery level or standard for age if only one reading); (b) shock; (c) bleeding (requiring blood transfusion); (d) encephalopathy; (e) liver impairment; (f) impaired kidney function; (g) myocarditis, pericarditis or clinical heart failure.
[†]Based on measured Dengue anti-NS1 IgG ELISA at Month 13 from first vaccination (Dengue Seropositive= ≥9EU/mL).
[‡] Cumulative incidence over 4 years from 13 months after the first vaccination.

Clinical Reviewer Comment: *There was a substantial increased RR for severe dengue, post Dengvaxia vaccination, in subjects who were dengue seronegative at M13 compared to subjects who were dengue seropositive at M13. These data support the limitation of Dengvaxia administration to persons who have laboratory confirmation of a previous dengue infection.*

8.4.4 Common Adverse Events

Solicited local and systemic adverse reactions were consistent across studies submitted to the BLA and therefore pooling of these data did not reveal additional points for consideration or safety signals (data not shown).

Unsolicited non-serious Adverse Reactions (unsolicited non-serious AE related to the vaccine by the study Investigator) were reported in 10% of adults and in 2.2% of subjects 9 to 17 years

of age. The frequency of occurrence of non-serious unsolicited reactions was higher in the Dengvaxia Group compared to the Control Group (10.0% in the Dengue Group vs 3.2% in the Control Group) in adults whereas frequency was comparable in the Dengvaxia Group and the Control Group in subjects aged 9 to 17 years (2.2% in Dengvaxia Group vs 1.2% in the Control Group). The most frequently reported unsolicited non-serious ARs were in the SOC "General disorders and administration site conditions" such as injection site hematoma, and injection site pruritus.

Clinical Reviewer Comment: *Most unsolicited non-serious AEs were of Grade 1 and Grade 2 intensity. Grade 3 unsolicited non-serious AEs were reported by 5.7% of subjects 9 to 17 years and by 7.5% of adult subjects. Unsolicited adverse events were reported at frequencies and intensities in both adolescent and adult subjects that are often observed in clinical trials of healthy populations. Specific safety concern related to Dengvaxia vaccination was the increased relative risk for severe dengue post-vaccination in subjects who were dengue seronegative at baseline.*

8.4.8 Adverse Events of Special Interest

Severe Allergic Reactions
There were no cases of anaphylactic reactions in any study. Less than 0.1% of the vaccinated subjects (n=5 subjects, 1 adult and 4 subjects aged 9 to 17 years) experienced at least 1 serious potential allergic reaction: 4 subjects experienced asthma or asthmatic crisis and had a relevant medical history of asthma, asthmatic bronchitis, or bronchial obstructive symptoms; 1 subject experienced urticaria and had a history of allergic rhinitis. Two of these serious potential allergic reactions (urticaria and asthma) were assessed as related to the study vaccine.

Viscerotropic or neurotropic adverse reactions
There were no cases of viscerotropic or neurotropic adverse reactions in any study.

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 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 associated 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 106 subjects enrolled in studies 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 dengue vaccine virus was detected in any sample. No safety concerns were noted in the relevant 2 subjects.

8.6 Safety Conclusions

The pooled analyses of safety data did not reveal any safety findings that were not identified in the analyses of the individual studies; nor did they characterize or quantify safety findings in any

manner that leads to safety conclusions that differ from the conclusions from each of the individual studies. The most important safety finding from the pooled analyses was of an increased relative risk for severe dengue in subjects who were dengue seronegative at baseline. Although the increased relative risk for severe dengue was observed in each of the three clinical efficacy endpoint studies, the pooled analyses showed that this risk was most clearly related to dengue serostatus at baseline.

9. ADDITIONAL CLINICAL ISSUES

9.1 Special Populations

9.1.1 Human Reproduction and Pregnancy Data

Pregnancies reported to have occurred in the post-marketing setting (because the product is approved outside the US) or were identified during participation in a clinical trial were followed for outcome. Post-marketing data identified a total of 56 pregnancies of which 24 resulted in live birth (none with congenital anomalies), 12 resulted in spontaneous abortion <20 weeks gestational age, and 2 resulted in fetal death at a gestation age ≥ 20 weeks without congenital anomaly. In clinical trials, a total of 1,707 pregnancies were reported of which 1,520 resulted in live birth, 17 of which were associated with a congenital anomaly (including 16 major congenital anomalies). Of the 187 cases not resulting in live birth, 13 cases were elective or therapeutic abortions,142 (8% of the reported pregnancies) were spontaneous abortions <20 weeks gestational age, 7 were ectopic or molar pregnancies, and 15 were intrauterine fetal death ≥20 weeks gestational age. Of the spontaneous abortions and the intrauterine fetal deaths 141/142 and 14/15 Dengvaxia exposures occurred prior to conception but after the last menstrual period plus 7 days.

Clinical Reviewer Comment: *The numbers of pregnancy exposure outcomes reported were greater in the clinical trials than in the post marketing setting as follow-up for outcome was likely to be more thorough in the context of clinical trials. The rates of non-live births and congenital anomalies are generally consistent with expected background rates for adverse pregnancy outcomes in the general population. Furthermore, based on the available evidence, symptomatic wild-type dengue infection during pregnancy is not associated with congenital malformations or low birthweight, although observational data suggest that maternal dengue infection may be associated with preterm birth, fetal distress during labor, fetal death in utero and late miscarriage (18-22). Adverse maternal outcomes described following dengue infection include hemorrhage during labor and retroplacental hematoma (18-22). Transient viremia has been reported following infection with dengue leading to maternal-fetal transmission via breastmilk or the placenta (23).*

Pre-clinical studies of Dengvaxia showed that in a developmental and reproductive toxicity study performed in female rabbits, in which the animals were administered a full human dose (0.5 mL) of Dengvaxia on two occasions before mating and three occasions during gestation, there was no teratogenic potential, and no effect on pre- or post-natal development. A reproductive toxicity study was performed in female mice. The animals were administered a full human dose (0.5 mL) of Dengvaxia on Day 6, 9 or 12 of gestation. No teratogenic potential was observed. Please see Section 4.3 for additional details.

These data were considered in product labeling for Dengvaxia (Section 8 of the package insert). Please see Section 11.5 for additional details.

9.1.2 Use During Lactation

Data are not available to assess the effects of Dengvaxia on the breastfed infant or on milk production/excretion. Dengvaxia was not evaluated during lactation in humans.

9.1.3 Pediatric Use and PREA Considerations

This submission required a Pediatric Study Plan (PSP) under PREA. The applicant was granted a waiver for birth to six months of age because studies are impossible or highly impractical [(e.g. the number of pediatric patients who would be both infected with Dengue and have laboratory confirmation of the infection is small and geographically dispersed) (section 505B(a)(4)(B)(i)]. A deferral for age six months to <2 years was granted because pediatric studies should be delayed until additional safety or effectiveness data have been collected (section 505B(a)(3)(ii)). Althought studies CYD23 and 14 included children down to 2 and 4 years of age, respectively, a deferral for 2 to <9 years was granted because further analysis of serological specimens from the subjects 2 through 8 years of age are needed to clarify the relationship between dengue sero-status pre-vaccination (using NS1 ELISA and statistical imputations) with vaccine efficacy and with risk for severe/hospitalized dengue. Therefore, because the biological product is ready for approval for use in adults before these analyses were completed a waiver was granted for < to 9 years of age (section 505B(a)(3)(A)(i). Provided the results of further analyses in 2 through 8 years are supportive, a study evaluating the safety and effectiveness in infants and children six months to 2 years of age will be required.

9.1.4 Immunocompromised Patients

Dengvaxia has not been studied in immunocompromised patients. It is reasonable to infer that the risk of a live attenuated viral vaccine in severely immunocompromised individuals could outweigh any possible therapeutic benefit given that such individuals are unlikely to mount an immune response to vaccination. This was considered in product labeling for Dengvaxia. Please see Section 11.5.

9.1.5 Geriatric Use

The safety and effectiveness of Dengvaxia have not been established in individuals age 65 years and older.

9.2 Aspect(s) of the Clinical Evaluation Not Previously Covered

9.2.1 Use of NS1 Ag ELISA to Evaluate Pre-vaccination Serostatus

The applicant conducted exploratory analysis to clarify the relationship between dengue serostatus at baseline and the relative risk for severe dengue post-vaccination. Because baseline sera had only been collected on approximately 10% of subjects, the sponsor developed an ELISA against the dengue virus protein NS1, a dengue antigen that was not contained in Dengvaxia, to test post-dose 3 sera and estimate baseline dengue serostatus based on the observation that subjects dengue seropositive at baseline had substantially higher post-dose 3 GMTs compared to subjects dengue seronegative at baseline. In contrast to the dengue neutralization assay $PRNT_{50}$, the NS1 assay can distinguish the immune response to vaccination from the immune response to natural dengue exposure. Therefore, the NS1 ELISA was performed 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 seropositive 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 52 displays the Hazard Ratio for hospitalized VCD stratified by baseline serostatus among all subjects 9 through 16 years of age from each clinical endpoint efficacy study and for all studies pooled.

Table 52: 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 $PRNT_{50}$ or imputed from NS1 Ag ELISA
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 seronegative population, vaccination increases the risk of hospitalized VCD.

Clinical Reviewer Comment: *There were substantial differences in the post-dose 3 GMTs between subjects who were dengue seropositive at baseline and those who were dengue seronegative at baseline (see Tables 14 and 27) in the CYD15 and CYD14 Phase 3 trials. These substantial differences in post-dose 3 GMTs suggested that the subjects' baseline serostatus (dengue seropositive or dengue seronegative) could be inferred from their post-dose 3 GMTs based on the $PRNT_{50}$ assay. The immunogenicity subset in the Phase 3 trials was approximately 10% of subjects enrolled in CYD15 and 20% of subjects enrolled in CYD14 and the cases of severe dengue were limited in number in both trials, resulting in few subjects with severe dengue who had a baseline dengue serostatus determined by the $PRNT_{50}$ assay. The applicant designed a case/cohort exploratory analysis which included all subjects in the immunogenicity subset; all subjects who had severe dengue at any time point from M0 to M60; and a randomly selected set of subjects who were not in the immunogenicity subset but did*

have post-dose 3 sera for GMT assessment (all subjects in each trial had 28 day post-dose 3 blood draws, per protocol). Each subject in this case/ cohort study was assessed by the NS1 IgG ELISA on their post-dose 3 sera and then multiple imputation methods were used to impute baseline serostatus, which was then correlated with the relative risk for severe dengue. A similar approach was used to impute baseline serostatus based on the $PRNT_{50}$ GMTs from the post-dose 3 sera. The results of each of these methods to impute baseline serostatus from post-dose 3 sera were similar and demonstrated a correlation between seronegative at baseline and increased relative risk for severe dengue. The correlation of baseline dengue serostatus and risk for severe dengue by these methods did not show different results from the analyses conducted using only subjects in the immunogenicity subset who developed severe dengue, however they provided further evidence of the strength of that correlation.

9.2.2 Discussion of Studies CYD28, CYD47 and CYD22

Studies CYD28, CYD47 and CYD22 provided descriptive safety and immunogenicity data in subjects 18-45 years of age. The intent of these data was to extend the age indication beyond the data in children 9-16 years of age for which clinical endpoint efficacy data were collected, to individuals 17-45. The sponsor proposed to infer effectiveness based on comparison of immunogenicity data in children 9-16 years to that in adults. However, based on the VRBPAC recommendations (see discussion in Section 5.4.1) the applicant revised the requested indication to include only children 9 through 16 years of age. Thus, given that the 3 clinical endpoint efficacy studies CYD15, CYD14, and CYD23 were considered sufficient to support the proposed age indication (by both VRBPAC and CBER, see recommendations for regulatory action in section 11.4) these data were no longer deemed necessary to support a regulatory decision and thus discussion of these studies is brief.

Design overview:

CYD28, CYD47 and CYD22 were phase 2, randomized, observer-blind studies that included adults (see Table 1 for description) with the descriptive safety and immunogenicity objectives and endpoints evaluated before and after each dose. While studies CYD22 and CYD28 enrolled children and adults, only immunogenicity data (by $PRNT_{50}$ ELISA) from adults enrolled in these studies are discussed. Dengue seropositive subjects were those with titers ≥ 10 (1/dilution) against at least one dengue serotype at baseline.

Immunogenicity Analyses:
Table 53 shows the pre-dose 1 and post-dose 3 GMTs by the $PRNT_{50}$ assay for subjects 9 through 16 years in clinical efficacy endpoint Studies CYD14 and CYD15 and for subjects 18 through 45 years in safety and immunogenicity Studies CYD22, CYD28 and CYD47.

Table 53: Geometric Mean Serum Neutralizing Antibody Titers (GMTs) by Serotype Among Vaccinated Dengue Seropositive Children and Adolescents 9-16 Years of Age from Efficacy Studies (CYD14, CYD15) and Among Vaccinated Dengue Seropositive Adults 18-45 Years of Age from Dengue 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)	482-485	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 Latin America (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; 32)
CYD22 India (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 Vietnam (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 PRNT50 which varied by serotype.

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

Clinical Reviewer Comment: *The inference of effectiveness being similar, for adult subjects in dengue-endemic regions who are dengue- immune at baseline, to the efficacy observed in adolescent subjects from CYD 14 and CYD 15, is supported by three observations. First, the post-dose 3 GMTs are similar between the adults in CYD22 and CYD47 and the adolescents in CYD15 and CYD14. Second, the GMTs in non-cases compared to cases in CYD15 and CYD14 supports an assertion that there is a relationship between higher post-dose 3 GMTs and increasing efficacy. Finally, it is biologically plausible that efficacy would be similar in adults as in adolescents based upon the characterization of dengue disease in adults being very similar to that in adolescents. It is noted, however, that the lack of a pre-specified, non-inferior on immunogenicity endpoint in CYD22 and CYD47 is a constraint on this inference, as is the uncertain relevance of these study populations to those living in dengue endemic areas in the US (e.g., Puerto Rico). Following discussion of these issues at the VRBPAC, the applicant ultimately decided to modify the proposed indication to include only individuals 9 through 16 years of age.*

10. CONCLUSIONS

Safety and efficacy data from studies CYD15, CYD14 and CYD23 and safety data derived from studies included in the integrated summary of safety (see Section 8) support the safety and effectiveness of Dengvaxia for individuals 9 through 16 years of age with laboratory confirmed previous dengue infection and living in dengue endemic areas. The indication for prevention of dengue disease due to serotypes 1,2,3, and 4 is supported by the submitted data with the important caveat that subjects be dengue seropositive pre-vaccination and have a laboratory confirmation of a prior dengue infection before being vaccinated. The additional limitation of indication to individuals residing in dengue endemic areas is necessary because Dengvaxia was not studied as a “traveler’s vaccine” and there are no efficacy data on Dengvaxia vaccination in dengue seropositive individuals who do not currently reside in a dengue endemic area. Dengvaxia vaccination of subjects who were dengue seronegative at baseline was associated with an increased relative risk for severe dengue post-vaccination and this is the reason for the limitation of indication to individuals with a laboratory-confirmed prior dengue infection.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

Risk-benefit considerations are presented in Table 54 below.

Table 54: Analysis of Decision Factors Relevant to the Risk-Benefit Assessment

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Dengue is a vector-transmitted infectious disease with global circulation affecting up to 3.9 billion individuals, with attack rates from 1-3% per year, affecting individuals of all ages. • Dengue infections are caused by four serotypes. Infection by one serotype does not confer durable protection to other serotypes. • Up to 60% of dengue infections are sub-clinical; 10% are severe; 5% require hospitalization for supportive care with 20,000 dengue-attributable deaths per year. • Severe/hospitalized dengue occurs more than 95% of the time with heterologous, second dengue infections.	• Dengue infection can result in serious, life threatening disease. • Immunity is serotype specific. • Severe/hospitalized dengue occurs with second, heterologous dengue infection and prevention of severe disease requires induction of effective immune responses against all four serotypes
Unmet Medical Need	• Supportive care is the mainstay of management of severe dengue infection. • There are no anti-viral products available to treat an acute dengue infection. • At present, no dengue vaccine is licensed in the US. • Vector control strategies are limited by the biting habits of the dengue mosquito vectors and have not been widely deployed or successful in limiting dengue transmission	• Dengvaxia would be the first dengue vaccine licensed and available in the US. • There will remain an unmet medical need for dengue prevention in individuals 0-8 years of age and >17 years of age because of the age indication of 9 through 16 years for Dengvaxia.
Clinical Benefit	• VE data from studies CYD14 and CYD15 demonstrate the effectiveness of Dengvaxia in individuals 9 through 16 years of age.	• VE data from studies included in the BLA support the effectiveness of Dengvaxia to prevent dengue disease caused by serotypes 1, 2, 3 and 4 in individuals 9 through 16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas.

Risk	• There is an increased RR for severe/hospitalized dengue post-vaccination in subjects 9 through 16 years of age who were dengue seronegative at baseline (RR of 2.44-6.25 based on pooled analyses). • There is a decreased relative risk for severe/hospitalized dengue post-vaccination in subjects 9 through 16 years of age who were dengue seropositive at baseline (RR 0.274-0.325 based on pooled analyses).	• The available evidence supports the safety of Dengvaxia in dengue seropositive individuals. • There is an increased relative risk for severe/hospitalized dengue post-vaccination for individuals who are dengue seronegative at baseline.
Risk Management	• The major risk for this vaccine is administration to individuals who are dengue seronegative at baseline (pre-vaccination #1). This risk can be mitigated by requiring laboratory confirmation of a prior dengue infection before administering the vaccine. This risk is also mitigated through use of Dengvaxia starting at age 9 years, since the proportion of individuals who have experienced at least one prior dengue infection increases with the age of the individual.	• Given the currently available assay methods to assess dengue serostatus, limiting the use of Dengvaxia to individuals age to 9 through 16 years and administering the vaccine only to individuals with laboratory confirmation of a prior dengue infection satisfactorily mitigate the risk of severe dengue infection related to vaccination.

11.2 Risk-Benefit Summary and Assessment

The clinical benefit of Dengvaxia in preventing dengue disease caused by any of the 4 serotypes is established by the results of 2 randomized, controlled observer-blind trials conducted in different dengue-endemic regions of the world. CYD 15, conducted in healthy children 9 through 16 years of age residing in Latin America, demonstrated an estimated VE of 60.8% (95%CI: 52.0; 68.0) against prevention of symptomatic, VCD. CYD14, conducted in healthy children 2 through 14 years of age residing in Asia, demonstrated an estimated VE of 56.5% (95%CI: 43.8; 66.4) against this same endpoint.

During the surveillance period extending to 59 months post-dose #1, a decreased RR for severe/hospitalized dengue disease was observed in vaccine recipients ages 9 through 16 years who were dengue seropositive at baseline, compared to placebo controls, based on pooled data from three clinical efficacy endpoint studies. Conversely, in vaccinated individuals who were dengue seronegative at baseline, efficacy was substantially lower in preventing dengue infections of any serotype, and vaccination was associated with an increased relative risk (2.43 (0.47;12.56) to 6.25 (0.81;48.32)) of severe/hospitalized dengue post vaccination. Therefore, the risk-benefit assessment for this vaccine is favorable for individuals who have laboratory confirmation of a prior dengue infection, pre-vaccination, and unfavorable in individuals who are dengue seronegative pre-vaccination.

The increased RR of severe/hospitalized dengue post vaccination in individuals who are dengue seronegative at baseline can be mitigated by limiting the use of Dengvaxia to individuals with laboratory confirmation of a dengue infection prior to vaccination since a substantial proportion of individuals in this age group residing in dengue endemic regions would have experienced a prior dengue infection. The average proportion of dengue seropositive 9-year old children can range, depending on dengue virus transmission intensity, from 10% (in areas of low transmission intensity) to 90% (in areas of very high transmission intensity) (24).

Risk mitigation can be promoted by appropriate Dengvaxia labeling to clearly state the limitations of the indication; a label warning about the potential for false positive serological testing in settings where other flaviviruses may be circulating; health care provider instructions on the limitations of indication; the risk for severe dengue post-vaccination in individuals who are dengue seronegative at baseline and the requirement for laboratory confirmation of a prior dengue infection before vaccinating with Dengvaxia.

There is currently no U.S.-licensed test for the purpose of confirming a previous history of dengue infection in an asymptomatic individual. To date, 31 companies have marketed 56 IgG ELISA tests and at least 7 rapid tests (Gabriela Paz-Bailey, VRBPAC Presentation, March 7, 2019). Available evidence for 17 of these tests (10 ELISAs and 7 RDTS) indicates that the estimated sensitivity (30-99%) and specificity (60-99%) vary substantially depending on the test used. Since few tests have been assessed independently, the sample sizes used to estimate test performance were variable (or information is unavailable), and specificity was not assessed by a uniform panel composition. These tests were calibrated for diagnosing dengue infection in symptomatic individuals with high IgG titers and not for the intended purpose of diagnosing previous infection in asymptomatic individuals. Cross-reactivity of these tests with other flaviviruses (e.g., zika virus, yellow fever, west nile virus, Japanese encephalitis and tick-borne encephalitis) has not been evaluated.

To inform the benefit-risk assessment of Dengvaxia, CBER analyzed the prevented and excess severe dengue cases in Puerto Rico for children 9 through 16 years of age over a 5-year post-vaccination period based on a "worst case scenario of assay performance." Per this analysis, CBER estimated that 175 cases of severe dengue would be prevented while 7 excess cases of severe dengue could occur; 875 cases of hospitalized dengue would be prevented while 35 excess cases could occur. (Please see Review Memo, Benefit-risk Assessment, Office of Biostatistics and Epidemiology, Dr. Hong Yang).

Additional factors that may affect the risk: benefit consideration for Puerto Rico or other U.S. territories where dengue is endemic are the rates of dengue seropositive individuals at baseline, pre-vaccination by regions within a dengue-endemic country; the availability of serological testing for dengue and the specificity of such tests for dengue infections in a setting where Zika, West Nile Virus (WNV) or other flavivirus infections may be common; and the pattern of serotype-specific attack rates, year by year. Each of these factors may impact the observed vaccine efficacy for a given year and in a region of a dengue-endemic country or territory.

The VE data from studies submitted in the BLA support the clinical benefit of Dengvaxia for prevention dengue disease due to any of the 4 serotypes in individuals 9 through 16 years of age who have laboratory confirmation of a prior dengue infection. Limitations to the indication to include only those with laboratory confirmation of prior dengue infection residing in dengue endemic areas (e.g. those with a higher pre-test probability to enhance positive predictive value of laboratory testing) were appropriate approaches to mitigate risk of vaccination of dengue seronegative individuals who could encounter an increased risk of severe/hospitalized dengue disease after vaccination.

11.3 Discussion of Regulatory Options

The regulatory options considered for this application were to approve the application for the indication as requested for 9 through 16 years of age, to request a complete response to address any potentially unresolved safety and/or effectiveness concerns for our review prior to approval, or to deny the approval.

The submitted data were considered sufficient to support the safety and effectiveness of Dengvaxia in children and adolescents 9 through 16 years of age for the prevention of dengue disease caused by dengue serotypes 1,2,3 and 4, in individuals who have laboratory confirmation of a previous dengue infection and who live in dengue-endemic areas.

11.4 Recommendations on Regulatory Actions

Traditional approval for 9 through 16 years for the indication of prevention of dengue disease due to any of the four serotypes in individuals with laboratory-confirmed prior dengue infection and residing in dengue endemic regions.

11.5 Labeling Review and Recommendations

Labeling discussions with the Applicant included the following considerations, resulting in submission of a final draft package insert on May 1, 2019, that was determined to be acceptable.

- The indication for Dengvaxia was restricted to individuals living in endemic areas. There were no data submitted to support an indication for individuals who live in non-endemic areas and travel to endemic areas.

- There are no FDA-cleared serological tests to determine a previous dengue infection and this fact is presented in the warnings section of the label.

- Given the demonstrated benefit of Dengvaxia for prevention of dengue in non-pregnant study population, and lack of evidence for clear risk in this population, a contraindication in pregnancy was not supported by the available evidence. A drug should be contraindicated only in those clinical situations for which the risk of use clearly outweighs any possible benefits (21CFR201.57). From a U.S. FDA regulatory perspective, lack of pre-licensure studies in pregnant women does not preclude use of vaccines during pregnancy. Should the sponsor seek a specific indication for use in pregnant women, adequate and well-controlled data supporting the safety and effectiveness and safety in this population would be necessary. Lack of a specific indication and usage statement about use of the product in pregnant women in the product labeling does not preclude use of these vaccines during pregnancy particularly if the vaccine is not contraindicated for use during pregnancy.

11.6 Recommendations on Post marketing Actions

The pharmacovigilance plan submitted by the applicant was considered acceptable by CBER and included routine pharmacovigilance for this product.