Individuals using assistive technology may not be able to fully access the information contained in this file. For assistance, please call 800-835-4709 or 240-402-8010, extension 1. CBER Consumer Affairs Branch or send an e-mail to: ocod@fda.hhs.gov and include 508 Accommodation and the title of the document in the subject line of your e-mail.

BLA Clinical Review Memorandum

Application Type	sBLA: Age Lowering Supplement
STN	125682/40
CBER Received Date	May 31, 2022
PDUFA Goal Date	Major amendment extension to June 30, 2023. (Originally March 31, 2023)
Division / Office	DVRPA/ OVRR
Priority Review (Yes/No)	No
Reviewer Name(s)	Ravi Goud MD MPH
Review Completion Date / Stamped Date	6/8/2023
Supervisory Concurrence	Ralph LeBlanc, M.D., PhD., Team Lead Maria Allende, M.D., Branch Chief
Applicant	Sanofi Pasteur, Inc.
Established Name	Dengue Tetravalent Vaccine, Live
(Proposed) Trade Name	Dengvaxia
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc.	Dengue Tetravalent Vaccine, Live (chimeric yellow fever dengue (CYD) virus serotypes 1, 2, 3, and 4)
Dosage Form(s) and Route(s) of Administration	0.5 mL administered to the deltoid region
Dosing Regimen	Three doses 6 months apart (at month 0, 6, and 12)
Indication(s) and Intended Population(s)	(Current) DENGVAXIA is a vaccine indicated for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4. DENGVAXIA is approved for use in individuals 9 through 16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas (Proposed) DENGVAXIA is a vaccine indicated for the prevention of dengue disease caused by dengue virus

	serotypes 1, 2, 3 and 4. DENGVAXIA is approved for use in individuals 6 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

Ab	antibody
AE	adverse event
AESI	adverse events of special interest
AP	Asia Pacific
CCID	cell culture infectious dose
CI	confidence interval
CSR	clinical study report
COS	Close-out study
CYD	chimera yellow fever dengue
DHF	dengue hemorrhagic fever
dil	dilution
DS	dengue screen
DSS	dengue shock syndrome
EU/mL	ELISA Units per milliliter
ELISA	enzyme linked immunosorbent assay
EMA	European Medicines Agency
FAS	full analysis set
FASE	full analysis set for efficacy
FASI	full analysis set for immunogenicity
FDA	Food and Drug Administration
GCP	good clinical practice
GMT	geometric mean of titers
GMTR	geometric mean of titer ratio
HR	Hazard Ratio
HVCD	Hospitalized virologically-confirmed dengue
IDMC	Independent Data Monitoring Committee
IS	Immunogenicity subset
Ig	immunoglobulin
LatAm	Latin America
LLOQ	lower limit of quantitation
LTFU	long-term follow-up
M	Month
MI	Multiple imputation

PD	post-dose
PRNT	plaque reduction neutralization test
prM	pre-membrane
PI	Prescribing information
RR	relative risk
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SP	Sanofi Pasteur
SEP	Surveillance Expansion Phase
SDD	Severe dengue disease
SVCD	severe virologically-confirmed dengue
Thr	Threshold
VCD	virologically confirmed dengue
VE	vaccine efficacy
WHO	World Health Organization
YF	yellow fever

1. Executive Summary

Dengvaxia is a live attenuated vaccine constructed using recombinant DNA technology by replacing the sequences encoding the pre-membrane (prM) and envelope proteins in the yellow fever (YF) 17D204 vaccine virus genome with those encoding for the homologous sequences of dengue virus serotypes 1, 2, 3, and 4, respectively. The applicant, Sanofi Pasteur (SP), submitted BLA 125682/40 to support lowering the age indication of the previously licensed vaccine, Dengvaxia, a live, attenuated, tetravalent, chimeric virus vaccine. Dengvaxia is currently 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. The sponsor is proposing lowering the age so Dengvaxia could be administered in individuals 6 through 16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas. Dengvaxia is not approved for use 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.

The age lowering submission contains no new clinical trials, instead the sponsor submitted the NS1 Close-out study (COS), a post-hoc study, which utilizes a case-cohort study design, and inferral (using NS1 laboratory test) and imputation methods to estimate baseline serostatus in previously conducted clinical trials in which subjects received either chimera yellow fever dengue (CYD) vaccine or placebo (CYD14, CYD15, and CYD23/57). The inferral/imputation approach increased the amount of data available for analyses and helps power the NS1 COS to evaluate safety and efficacy in seropositive 6 to 8 year old individuals, the age group and serostatus being considered for inclusion in the Dengvaxia indication. This was necessary as only a portion of subjects in the original studies had blood samples drawn to assess baseline serostatus (approximately 10%, n=3800 across all age groups had serostatus assessed at baseline). Consideration of efficacy and risk by serostatus is necessary for Dengvaxia, as the initial approval was limited to use in seropositive 9 to16 year old individuals due to the observation of an increased risk of severe dengue in vaccinated individuals who were seronegative at baseline.

The NS1 COS evaluated vaccine efficacy and risk according to baseline serostatus which was inferred/imputed based on the Dengue anti-non-structural protein 1 (NS1) immunoglobulin G (IgG) enzyme-linked immunosorbent assay (ELISA) performed on month 13 (M13) blood samples. The NS1 COS categorized serostatus in the following ways, inferred:

- Dengue anti-NS1 IgG ELISA assay readout at M13 (seronegativity defined as an anti-NS1 titer < 9 EU/mL and seropositivity as an anti-NS1 titer ≥ 9 EU/mL).
- Strict seropositive classification (strict seropositivity defined as anti-NS1 titer ≥ 50 EU/mL at M13).

And imputed (or measured for those subjects with blood samples drawn at baseline):

- Measured or imputed plaque reduction neutralization test (PRNT50) at baseline (M0).
- Measured or imputed PRNT90 at M0.

The NS1 COS conducted many analyses and sub-analyses for different age strata and by serostatus, but the analyses most pertinent to lowering the age indication are estimates of vaccine efficacy and safety in the population of 6 to 8 year old individuals

that are designated as seropositive at baseline. The NS1 COS estimated vaccine efficacy against Virologically Confirmed Dengue (VCD) post dose 3 and in the active phase (from M13 to M25), and estimated the safety risks of Hospitalized VCD (HVCD) and Severe VCD (SVCD) during the entire study period in 6 to 8 year old individuals designated as seropositive at baseline.

In the NS1 COS, the Vaccine Efficacy (VE) amongst those designated seropositive in the 6 to 8 year old group ranged from 55.8 to 67.3 for the four different serostatus inferral and imputation methods. In the original clinical trials considered for initial licensure of Dengvaxia, the success criterion for efficacy was a Lower Bound of the Confidence Interval (LBCI) greater than 25%, and in the NS1 COS, the analysis of VE using the imputation methods for determining serostatus yielded a LBCI for VE greater than 25%, while the LBCI for the NS1 inferral approaches were 1.8 and 6.2. These point estimates and the CIs, however, are acceptable and show efficacy as this post-hoc analysis did not prespecify a LBCI >25% and was not powered to exceed this threshold.

In comparison, VE estimates for the 9 to 16 age range were from 76.7 to 79.0 and CIs were small with the LBCI greater than 25%, which is similar to the findings in the original approval, which had a VE of 80.6 with a 95%CI of (50.7; 93.2) in dengue seropositive individuals aged 9 to 16 years of age. The consistency of results lends support to the validity of the NS1 analyses. Findings for the combined 6 to 16 year old group are similar, ranging between and 75.6. and 77.7 with LBCI >25%; this is reassuring, as efficacy is shown to be adequate for the whole age range proposed by the sponsor's new indication.

The NS1 COS safety analyses demonstrated no increased risk of HVCD or SVCD in subjects 6 to 8 years old, as for all the inferral and imputation based analyses of HVCD and SVCD in seropositive 6 to 8 year old individuals, the point estimates were below 1, and Dengvaxia was protective. In addition, for 7 out of 8 of the inferral/imputation based analyses, the 95% confidence interval (CI) for the risk of HVCD and SVCD did not cross 1. For one of the SVCD analyses that did have a CI that crossed 1(the NS1 threshold [Thr] 9 SVCD analysis) it just slightly crossed 1 with a higher bound of 1.053.

These findings are in line with the analyses which supported the original approval in seropositive individuals 9 to 16 years old, as in this population, there was no increased risk of SVCD and HVCD. Furthermore, in seropositive subjects aged 6 to 8 years in the immunogenicity subset (IS), the RR estimate was 0.378, which is consistent with the NS1 COS analysis point estimates for seropositive 6 to 8 year old individuals, as these ranged from 0.210 to 0.404. Similarly, the risk of SVCD in NS1 COS estimates varied between 0.223 and 0.400, which is consistent with the RR estimate in the IS of 0.360.

These findings contrast with findings in analyses of the seronegative population. In the 6 to 8 year old seronegative group, point estimates of the risk of HVCD varied between 1.531 and 1.949, and point estimates of the risk of SVCD were between 2.483 and 2.752. These analyses indicate Dengvaxia is not safe for use in seronegative 6 to 8 year old individuals. In addition, efficacy is lower in seronegative populations as point estimates of VE were less than 50% with 95% CIs crossing zero.

Taken together, the consistency of point estimates for the lack of increased risk of HVCD and SVCD in seropositive 6-8 years subjects; the similarity of findings with analyses of seropositives in the IS analyses, and the contrasting elevated risk observed in

seronegative 6 to 8 year old individuals indicate the vaccine is protective in seropositive 6 to 8 year old individuals, and that there is no increased risk of HVCD or SVCD in this population. Again, these findings are consistent with the findings of efficacy, and the lack of a safety concern in seropositive 9 to 16 year old individuals, which was the basis of the original approval.

Of note, this was not the case in NS1 COS analyses of seropositive 2 to 5 year old individuals. In these analyses, the findings were not supportive of the vaccine, and did not demonstrate a decreased risk of SVCD and HVCD, rather, 3 out of 4 analyses of HVCD had CIs that crossed 1, and for SVCD analyses, all four CI crossed one, with one point estimate also being greater than one at 2.201.

In summary, the NS1 COS analyses in dengue seropositive subjects 6 to 8 years old pre-vaccination demonstrated efficacy against VCD without any increased risk in HVCD or SVCD. Conversely, in the 6 to 8 year old subjects who were dengue seronegative pre-vaccination, an increased risk of HVCD and SVCD was observed. This is similar to findings in the original approval in 9 to 16 year old individuals which was the basis of limiting of the indication for Dengvaxia to individuals residing in dengue endemic regions, and who have laboratory confirmation of a previous dengue infection. CBER recommends approval of lowering the age of Dengvaxia to include 6 to 8 year old dengue seropositive individuals, so the indication would cover individuals 6 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

This supplement contains the NS1 COS, which is a post-hoc study of the three clinical efficacy endpoint studies: CYD23/57 in Thailand, CYD14 in southeast Asia Pacific countries, and CYD15 in Latin American countries, which supported the original approval of Dengvaxia in 9 to 16 year old individuals.

Subgroup analyses assessed vaccine efficacy and safety by age (2-5 years, 6-8 years, 9-16 years, and 6-16 years cumulatively) and measured or designated dengue serostatus at baseline pre-vaccination (seropositive or seronegative).

In the original studies, race and ethnicity were not evaluated as factors that could impact effectiveness, since 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.” For a further discussion of Demographics, please refer to Section 6.1.10.1.1.

1.2 Patient Experience Data

As conveyed in the table below, no patient experience data were submitted to this supplemental BLA.

Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
☐	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
☐	Patient-focused drug development meeting summary	
☐	FDA Patient Listening Session	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☒	**If no patient experience data were submitted by Applicant, indicate here.**	
Check if Considered	**Type of Data**	**Section Where Discussed, if Applicable**
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting	
☐	FDA Patient Listening Session	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

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), which are transmitted by *Aedes aegypti* mosquitos and other members of the Aedes mosquito family. All four dengue serotypes are present each year in most countries, but one or two dengue serotypes are usually dominant. It is estimated that 390 million dengue infections occur annually worldwide, which results in approximately 100 million with clinical manifestations, 500,000 hospitalizations, and 20,000 deaths.[1] In the Americas in 2022, there were approximately 1.4 million confirmed dengue cases, 4,500 severe cases, and 1,300 deaths.[2]

1 Bhatt S, Gething PW, Brady OJ, et al. The global distribution and burden of dengue. Nature 2013; 496:504-7
2 Pan American Health Organization. Dengue. Available at: https://www.paho.org/data/index.php/en/mnu-topics/indicadoresdengue-en.html. Accessed May 22, 2023

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). In the United States (US) and its territories, dengue is considered endemic in Puerto Rico, Guam, Samoa, and the US Virgin Islands, but locally acquired cases have also emerged at the Texas-Mexico border and in Hawaii.[3] Since dengue competent vectors are found in many states in the US, there is the potential for dengue to become endemic in the US. In fact, cases generally have been on the rise in the US, both in the endemic territories, and among travelers returning to the US from other countries.[4]

Dengue Infection and Disease

Dengue infection occurs when the bite of a competent vector injects the dengue virus into the extravascular tissue, where the virus infects primarily dendritic cells. After draining lymph nodes become infected, the individual becomes viremic and possibly febrile for a period of 3-5 days. Dengue disease can manifest across a spectrum of clinical illness from the asymptomatic, which occurs in up to 60% of infections, to non-specific febrile illness, and to severe, fatal hemorrhagic disease.

WHO categorizes severe dengue disease into four grades of severity. The most severe forms, grade III and IV Dengue Hemorrhagic Fever (DHF), are known as dengue shock syndrome (DSS), and occur in less than 1% of patients. Criteria for DSS include sever plasma leakage, severe hemorrhage, and severe organ impairment.[5]

Approximately 95% of DHF cases occur with a second dengue infection, and this is almost always due to a heterologous serotype. The mechanisms leading to DHF are unclear, but Antibody Dependent Enhancement (ADE) is thought to play an important role. An initial infection induces potent humoral and cellular immune responses that generally prevent a second infection by the same serotype, but these primary dengue infections can induce broadly cross-reactive, but weakly binding antibodies against heterologous serotypes. A secondary, heterologous dengue infection, can then trigger ADE which results in DHF.[2,3]

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

There are no approved antiviral treatments for dengue, and treatment is generally supportive. This includes, 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.

Prevention measures include preventing mosquito bites through personal protection and vector control strategies.

2.3 Safety and Efficacy of Pharmacologically Related Products

Dengvaxia is a first in class vaccine which was licensed in the U.S. in May of 2019 and is approved for prevention of dengue disease caused by dengue virus serotypes 1, 2, 3, and 4. There are limitations however, as it is approved for use only in individuals 9

3 Brady OJ, Gething PW, Bhatt S, et al. Refining the global spatial limits of dengue virus transmission by evidence- based consensus. PLoS Negl Trop Dis 2012;6:e1760.
4 Wong, Joshua M et al. "Dengue: A Growing Problem With New Interventions." *Pediatrics* vol. 149,6 (2022): e2021055522. doi:10.1542/peds.2021-055522
5 Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control: New Edition. Geneva 2009.

through 16 years of age with laboratory-confirmed previous dengue infection, and who live in endemic areas. Amongst this population, from the original review, vaccine efficacy is 80.6 95%CI (50.7;93.2).

Another dengue vaccine has been developed by Takeda, Qdenga. The BLA is currently being reviewed by FDA, and it has received a positive EMA opinion for individuals over 4 years of age.

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.

From Dengvaxia's first approval in 2015 until 31 May 2022, a total of 2,946,342 doses have been distributed worldwide. Assuming that patients may have received from 1 to 3 doses in accordance with the recommended schedule listed in the prescribing information (PI) during the cumulative period, the estimated number of patients who may have received CYD Dengue vaccine is between 982,114 and 2,946,342. Most vaccine recipients were 9-16 years of age. Initially, the vaccine was utilized in high seroprevalence settings regardless of serostatus, but in 2018 WHO revised their position to recommend use only in individuals with evidence of a past dengue infection.[6]

The applicant has a pharmacovigilance plan in place to continuously evaluate the risks and benefits of Dengvaxia. This includes routine and enhanced passive surveillance, and an ongoing pregnancy registry. No new safety issue due to Dengvaxia has been identified from post-marketing use of the vaccine as of 07 March 2020. The most frequently reported AEs are consistent with the current PI.

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

- 19 May 2019 – FDA approved Dengvaxia for use in individuals 9 through 16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas.
- 28 Aug 2020 – Sanofi submitted STN 125682/21 which included the requirements to close-out PREA related post marketing commitments 1 through 4 and expand indication to include 6 to 8 year old individuals
- 17 Nov 2020 – CBER provided feedback regarding improvements to the supplements for resubmission
- 07 Dec 2020 – Sanofi sent a draft Reviewer's Guides via email to CBER for review and feedback
- 25 Jan 2021 – CBER feedback received regarding the Risk Management Plan (RMP)
- 23 Feb 2021 – Sanofi submitted a proposed plan for resubmission of the supplements and closure of outstanding post marketing commitments to IND 11219 (seq 0277)
- 24 Jun 2021 – CBER feedback received regarding Sanofi's proposed plan for

6 Thomas, Stephen J, and In-Kyu Yoon. "A review of Dengvaxia®: development to deployment." *Human vaccines & immunotherapeutics* vol. 15,10 (2019): 2295-2314. doi:10.1080/21645515.2019.1658503

supplement resubmission and post marketing commitment closure

- 12 Nov 2021 – Final CBER feedback regarding Sanofi's proposed plan for supplement resubmissions
- 31 May 2022 – Sanofi resubmitted age lowering supplement as 125682/40

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

The application was adequately organized and integrated to permit a 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

Covered clinical study (name and/or number):
Was a list of clinical investigators provided? ☐ Yes ☐ No (Request list from applicant)
Total number of investigators identified: >1000
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): 0 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

Please see the CMC review.

4.2 Assay Validation

Please see the CMC review.

4.3 Nonclinical Pharmacology/Toxicology

No new nonclinical pharmacology or toxicology data was submitted as part of this submission, so no issues identified

4.4 Clinical Pharmacology

No new clinical pharmacology data was submitted as part of this submission, so no issues identified.

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

This clinical reviewer discussed the NS1 COS methodology and results extensively with the statistical reviewer. The statistical reviewer ultimately agreed that the vaccine efficacy and safety results based on multiple imputation methods from the Sponsor to designate serostatus were likely robust. The statistical and clinical reviewer communicated with the sponsor to clarify aspects of the analyses, and requested additional analyses to evaluate the MI designation of serostatus, and how this affected the robustness of efficacy and safety findings in seropositive individuals. While several potential issues were noted by the statistical reviewer after the applicant was asked to perform sensitivity analyses, alternative analyses were conducted by both the applicant and statistical reviewer that were based on an imputation-free approach to avoid the impact of these potential issues; these results were found to be similar to the originally reported results regarding vaccine efficacy, and the risk of SVCD or HVCD. Please see the Statistical review for details.

4.6 Pharmacovigilance

The sponsor provided an up-to-date narrative and analysis of post market Dengvaxia adverse event reports in children 6 to 8 years old. As of 31 May 2022, no cases were retrieved in the 6-to-8-year age group in Thailand, Argentina and the EU, countries where the vaccine has been approved for this age group. However, there were 21 reports in which the vaccine was administered off-label in other countries where the vaccine is not yet approved for this age group. Out of 21 reports, 14 are non-serious cases of using Dengvaxia off-label in children 6-8 years of age with no ensuing adverse

events. Two cases were assessed as serious (one fatal), and described severe dengue leading to death, and a case of submandibular cellulitis on the same day as receiving Dengvaxia that recovered. No safety signals were identified.

A cumulative review of Dengvaxia conducted in the VAERS database, and data mining using Empirica Signal 8.0 was performed for Dengvaxia on 26 April 2023, which did not identify any new safety concerns.

The sponsor has submitted an updated Pharmacovigilance Plan with the latest version of their Risk Management Plan (RMP) Version 7.0 implemented. The sponsor continues to monitor the safety of Dengvaxia through routine and enhanced pharmacovigilance activities, Post Authorization Safety and Efficacy Studies (PASS/PAES), and specific clinical studies. Most of the studies listed in the original Pharmacovigilance plan have been completed. The following table lists those studies that are currently ongoing or planned.

Table 1. Current and Planned safety studies

STUDY	OBJECTIVES	MILESTONES
DNG15	Evaluate safety profile of Dengvaxia	Ongoing European Union (EU) study– update with each Periodic Benefit Risk Evaluation Report (PBRER) or RMP; study report 12/31/2025
DNG16	Safety profile of Dengvaxia in inadvertently exposed pregnant women and their offspring	Planned – update with each PBRER/RMP; study report 12/31/2023
DNG00044	Safety profile of Dengvaxia following severe and hospitalized severe dengue disease	Planned – update with each PBRER/RMP; study report 12/31/2026
CYD50	Safety and immunogenicity in stable HIV+ adults under antiretroviral therapy	Ongoing – update with each PBRER/RMP; study report 9/30/2023

Overall, postmarketing experience did not indicate any new safety issues for Dengvaxia when used in children 6 to 8 years of age. DPV agrees with routine and enhanced pharmacovigilance activities, the ongoing postmarketing studies, and limiting use of Dengvaxia to seropositive individuals with corresponding labeling of risk of severe/hospitalized dengue in seronegative individuals.

5. Sources of Clinical Data and Other Information Considered in the Review

5.1 Review Strategy

The NS1 COS is a post-hoc study, which utilizes a case-cohort study design to analyze data collected in the original clinical trials submitted to the original BLA, supplemented with some additional follow-up data. The clinical study report (CSR) for the NS1 COS, appendices, and the supporting efficacy and safety summaries, proposed labeling, financial disclosure sections of the application, and various communications with the Sponsor were reviewed.

The NS1 COS is generally described in section 6, and the most pertinent analyses from this study, and the clinical summaries and overview are presented in the integrated analysis of efficacy (section 7) and the integrated analysis of safety (section 8).

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

eCTD Module 1: 1.3.4 Financial Certification and Disclosure, 1.14.1 Draft Labeling

eCTD Module 2: 2.5 Clinical Overview 2.7.3 Clinical Summary Efficacy, 2.7.4 Clinical Summary of Safety

eCTD Module 5: 5.3.5.4 Other Study Reports (NS1 COS report)

IR responses: 125682/40.3, 125682/40.6 ,125682/40.7, 125682/40.8, 125682/40.9, 125682/40.10, 125682/40.11, 125682/40.12, 125682/40.13, 125682/40.14, 125682/40.15, 125682/40.16, 125682/40.17, 125682/40.18

5.3 Table of Studies/Clinical Trials

Table 2: Overview of original studies included in the NS1 COS

Study	Study design and status	Data contribution to the current submission

CYD14	**Ph III, Efficacy Study**
	• N =10 275, 2-14 years in Thailand, Indonesia, Malaysia, Philippines, Vietnam
	• CYD or placebo at 0, 6, 12 months
	5 years follow-up after the last injection at month 12 (6-year follow-up)
	• Study completed
		• **Integrated analyses for safety (2.7.4), immunogenicity and efficacy (2.7.3):**
		  • Immunogenicity: 6-8 and 2-5, 9-17 years age groups
		  • Efficacy: 6-8 and 6-16, 2-5, 9-16 years age groups
		  • Safety: 6-8 and 6-17, 2-5, 9-17 years age groups
		• **NS1 Supplemental Analyses:**
		  • 6-8 and 2-5, 6-16 and 9-16-years age groups

CYD15	**Ph III, Efficacy Study**
	• N =20 869, 9-16 years in Brazil, Colombia, Honduras, Mexico, Puerto Rico
	• CYD or placebo at 0, 6, 12 months
	5 years follow-up after the last injection at month 12 (6-year follow-up)
	• Study completed
		• **Integrated analyses for safety (2.7.4), immunogenicity and efficacy (2.7.3):**
		  • Immunogenicity: 9-17 years age group
		  • Efficacy: 6-16, 9-16 years age groups
		  • Safety: 6-17, 9-17 years age groups
		• **NS1 Supplemental Analyses:**
		  • 6-16, 9-16 years age group

CYD23/57	**Ph IIb, Proof of concept efficacy study** • N =4002, 4-12 years in Thailand • CYD or placebo at 0, 6, 12 months 5 years follow-up after the last injection at month 12 (6-year follow-up) • Study completed	• **NS1 Supplemental Analyses:** • 2-5 and 6-8, 6-16 and 9-16 years age groups

*adapted from page 8 of the reviewer guide

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

6.1 Trial #1

NS1 Close-out study (NS1 COS), which is a post-hoc analysis of the Risk of Symptomatic Virologically-confirmed Dengue, Dengue Hospitalization, and Severe Dengue According to Dengue Serostatus in CYD Vaccine Efficacy Trials.

6.1.1 Objectives

The NS1 COS evaluated vaccine efficacy and risk according to baseline serostatus as determined by a Dengue anti-non-structural protein 1 immunoglobulin G enzyme-linked immunosorbent assay performed on M13 blood samples. The study identified its primary objective as: To compare the risk of dengue hospitalization occurring after M0 or after M13 (including Active and Hospital Phase) in CYD dengue vaccine versus control study subjects aged ≥ 9 years at enrollment and classified as dengue seronegative.

Reviewer Comment: The study has over 40 secondary and exploratory objectives, and these encompass analyses of safety and efficacy broken down by different age strata, and dengue seropositive or seronegative status. The safety objectives analyze the occurrence of dengue hospitalization (HVCD), and severe VCD (SVCD) after CYD vaccination compared to control study subjects. The efficacy objectives analyze the ability of CYD dengue vaccine to prevent symptomatic VCD. Much of the NS1 COS separates analyses by the study population greater than or equal to 9 years old, and the population less than 9 years of age, but the key analyses supporting the age lowering indication focus on estimates of vaccine efficacy and safety in the population of 6 to 8 year old individuals that are designated as seropositive at baseline. Serostatus was inferred/imputed through multiple methods used by the Sponsor. Please see sections 7 and 8, the integrated analyses of efficacy and safety, respectively, for an assessment of data and analyses central to the argument for lowering the age indication for Dengvaxia. Section 6 will describe general aspects of the NS1 COS and some of the analyses that serve as useful background information, or as points of comparison.

6.1.2 Design Overview

This NS1 Close-out study is a pooled, post-hoc, case-cohort analysis of data from clinical trials evaluating the safety and efficacy of CYD dengue vaccine. This comprises CYD14, which concluded 21 November 2017 and included 5 years of long-term follow-up (LTFU), CYD15, which concluded 05 March 2018, and also included 5 years LTFU, and CYD23/CYD57, which concluded 21 December 2015, and also included 5 years LTFU.

A case-cohort design (including all subjects with outcomes of interest and a randomly selected “sub-cohort”) was used to obtain efficacy and risk estimates according to dengue serostatus. The sub-cohort included approximately 10% of the entire study cohorts of CYD14, CYD15, and CYD23/57. All subjects with outcomes of interest (symptomatic VCD, all hospitalized dengue, and all severe dengue) from the original studies were retained in the NS1 COS for analysis.

The NS1 COS was necessary to assign serostatus to study participants and power

the analysis in baseline seropositive individuals 6 to 8 years of age because only approximately 12% of participants in CYD14 and CYD15 had baseline serostatus assessed. The sponsor, however, could infer and impute baseline serostatus due to the availability of 28 day post-dose-3 NS1 laboratory test values in all subjects, and the observation of a differential immunological response to vaccination that was observed in the original studies between individuals who were dengue seropositive and dengue seronegative at baseline. Specifically, individuals in the clinical trial immunogenicity subsets who were seropositive at baseline had substantially higher post-dose 3 plaque reduction titers compared to individuals who were seronegative at baseline.

The study evaluated dengue outcomes according to dengue serostatus based on the analysis of blood samples collected from subjects in the 3 efficacy studies (CYD14, CYD15, and CYD23/57). Subjects in these studies received either CYD dengue vaccine or placebo, and the analysis of dengue outcomes were conducted according to dengue serostatus. The imputation analyses were performed from M0 and M13 onwards, while for the inferral analyses they were performed from M13 onwards, as the laboratory test that is the basis of the inferral was assessed at M13. The dengue serostatus classification was performed using the following approaches:

- Measured or imputed plaque reduction neutralization test (PRNT50) at baseline (M0).
- Dengue anti-NS1 IgG ELISA assay readout at M13 (seronegativity defined as an anti-NS1 titer < 9 ELISA Units per milliliter (EU/mL) and seropositivity as an anti-NS1 titer ≥ 9 EU/mL).

Additional sensitivity analyses were:

- Strict seropositive classification (strict seropositivity defined anti-NS1 titer ≥ 50 EU/mL at M13).
- Measured or imputed PRNT90 at M0.

For efficacy analyses, data from M0-M25 as well as M13- M25 were used for the multiple imputation (MI) approach, and data from M13-M25 was used for NS1 at M13 approach. Efficacy estimates obtained from M0 onwards and M13 onwards are consistent with the per-protocol (M13-M25) and intention-to- treat analysis (M0-M25) in the efficacy trials.

For analyses of the risk of hospitalized VCD cases and severe VCD cases, data M0-M72 were used for the MI approach. Data from M13-M72 was used for both MI and NS1 at M13 analyses.

<u>Reviewer Comment:</u> The age lowering submission contains no new clinical studies, instead the NS1 COS, a post-hoc study utilizes a case-cohort study design, and inferral (using the NS1 laboratory test) and multiple imputation (MI) methods to estimate baseline serostatus in previously conducted clinical trials (CYD14, CYD15, and CYD23/57). This increases the amount of data available for analyses and helps power the NS1 COS to evaluate safety and efficacy in seropositive 6 to 8 year old individuals, the age group and serostatus being considered for inclusion in the Dengvaxia indication.

6.1.3 Population

The study report refers the reader to the CSRs for the individual trials, as new studies were not conducted.

Reviewer Comment: From the original approval clinical review memo:

CYD15: A total of 20,869 subjects 9-16 years old were enrolled and randomized in a 2:1 ratio in South and Central American countries.

CYD14: A total of 10,275 subjects 2-14 years old were randomized in a 2:1 ratio in Asian countries.

CYD23: A total of 4,002 subjects 4-11 years old were randomized in a 2:1 ratio in Thailand.

The original review found the enrolled populations acceptable, and that inclusion and exclusion criteria were acceptable. The review did note that CYD14 and CYD15 were not powered to assess efficacy on a per country basis.

As the original review found enrolled populations acceptable, the populations are also acceptable for the NS1 COS post-hoc analysis.

6.1.4 Study Treatments or Agents Mandated by the Protocol

CYD dengue vaccine or placebo was administered as part of the source studies, no new interventions were administered.

Reviewer Comment: Subjects were administered CYD or placebo at 0, 6, and 12 months in the original studies.

From the original approval clinical review memo CYD vaccine is described as:
CYD (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 log10 cell-culture infectious dose 50% (CCID50) 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

6.1.7 Surveillance/Monitoring

Reviewer Comment: From the original approval clinical review memo, CYD14, CYD15, and CYD23 had similar surveillance/monitoring, which consisted of 3 phases.

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 a minimum of 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 starting 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 reverse transcriptase polymerase chain reaction (RT-PCR) or Non-structural protein 1 (NS1) antigen testing. During the second year of the hospital phase, subjects had the option to reconsent to participate in the Surveillance Expansion Phase (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: 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.

6.1.8 Endpoints and Criteria for Study Success

The NS1 COS lists the primary endpoints, which are for safety, as:

- Occurrence of dengue hospitalization after M0 or after M13 (including Active and Hospital Phase) in study subjects of any age at enrollment and classified as dengue seronegative.
- Occurrence of dengue hospitalization after M0 or after M13 (including Active and Hospital Phase) in study subjects who were younger than 9 years of age at enrollment and classified as dengue seronegative.

It also lists the secondary endpoints, which are for efficacy, as:

- Occurrence of symptomatic VCD cases between M0 and the end of Active Phase and between M13 and end of Active Phase, regardless of severity and dengue serotype in subjects 9 years of age and older at enrollment who were classified as dengue seronegative.
- Occurrence of symptomatic VCD cases between M0 and the end of Active Phase and between M13 and end of Active Phase, regardless of severity and dengue serotype in subjects of any age who were classified as dengue seronegative.
- Occurrence of symptomatic VCD cases between M0 and the end of Active Phase and between M13 and end of Active Phase, regardless of severity and dengue serotype in subjects younger than 9 years of age at enrollment who were classified as dengue seronegative.

Reviewer Comment:
As previously stated, the NS1 COS conducted multiple analyses, and although it identified the endpoints listed above as the primary and secondary endpoints, the actual endpoints of interest were, for efficacy:

- *Occurrence of symptomatic VCD cases between M13 and end of Active Phase in subjects 6 to 8 years of age at enrollment who were classified as dengue seropositive.*

And for safety:

- *Occurrence of HVCD cases during the entire study period in subjects 6 to 8 years of age at enrollment who were classified as dengue seropositive.*
- *Occurrence of SVCD cases during the entire study period in subjects 6 to 8 years of age at enrollment who were classified as dengue seropositive.*

These analyses were presented in the Sponsor's clinical overview (CO) document.

The NS1 study does not specify criteria for success, but the clinical overview document states the imputation analyses are conclusive if CI for VE do not cross zero, and if HR estimates do not cross 1. This is acceptable, as the NS1 COS did not specify and was not powered to evaluate the efficacy success criteria identified in the original BLA of LBCI for VE >25%.

6.1.9 Statistical Considerations & Statistical Analysis Plan

M0 and M13 Dengue anti-NS1 titers were evaluated in all subjects included in the CYD14 and CYD15 immunogenicity subsets. Misclassifications were estimated for the CYD dengue vaccine and placebo groups and for cases and non-cases when using a threshold of < 9 EU/mL for seronegativity. Differences in misclassification between groups (vaccine vs. placebo, vaccine cases vs. vaccine non-cases, etc.) were tested using Chi-square test or Fisher's exact test as appropriate. Differences in misclassification between cases and non-cases were compared between the CYD Dengue Vaccine Group and the Placebo Group using the Breslow-Day test. Additionally, the effect of the CYD vaccine on the Dengue anti-NS1 titer was evaluated by estimating the geometric mean titer (GMT) ratio post-vaccination versus pre-vaccination GMT, and by comparing to the GMT ratio post-placebo injection versus pre-placebo injection. This was evaluated using a student's T-test. This was done overall and for cases and non-cases and could be evaluated by strata of interest.

A prediction/imputation method was used to impute PRNT serostatus at baseline for subjects included in the Close-out case-cohort analysis that did not have baseline values. The accuracy of the imputation approach was cross-validated for predictability of actual baseline PRNT50 serostatus by applying the imputation approach to the subset of subjects with measured PRNT50 at M0.

The risk of dengue hospitalization in CYD dengue vaccine versus control study participants could then be estimated by serostatus. The principal analyses determined serostatus by M0 PRNT50 (either measured or imputed).

Multiple imputations with logistic regression with 10 iterations were used to impute baseline serostatus as the dependent variable and M13 anti-NS1 titers and other variables as predictors. Then in each of the 10 iterations of MIs, a Prentice's weighted Cox regression model was used to estimate the risk and efficacy in the expanded case-cohort. The Prentice model, including the vaccine group as covariate, was used to calculate the hazard ratios (HR). The 95% CI of HR and p-value associated with Wald-type test statistic was calculated using the variance estimator by Barlow. Rubin's rule was then used to combine the hazard ratio from 10 iterations to obtain the final estimate of risk and efficacy.

Thus, 2 sets of analyses were produced using PRNT50 at M0 to determine serostatus:

- MI approach for post-M0 events (MI M0)
- MI approach for post-M13 events (MI M13)

In addition, complementary analyses determined serostatus by anti-NS1 ELISA levels at M13 and estimated the risk of dengue hospitalization and of severe dengue, as well as VE.

Sensitivity analyses determined serostatus by other approaches ("strict seropositive", and measured / imputed PRNT90 at M0 classifications) and were also used to estimate the risk of dengue hospitalization, the risk of severe dengue, and VE, in the expanded case-cohort.

Hazard ratio and corresponding 95% CI were tabulated and presented graphically with forest plots.

<u>Reviewer Comment:</u> For a more detailed description and analysis of the statistical plan, please see the statistical review. The clinical review team communicated extensively with the statistical review team, and the methodology used by the Sponsor was deemed robust.

Table 3, below, shows the accuracy of the imputation methods when the imputed serostatus is compared to those individuals for whom baseline serostatus is available.

Table 3: Cross-validation to assess performance of logistic regression used in multiple imputation in predicting M0 PRNT50 serostatus using NS1 M13 titer and other covariates

			Observed M0 PRNT50 Serostatus		
			Seropositive	***Seronegative***	***Total***
All subjects	*Predicted M0 PRNT50 Serostatus*	*Seropositive*	*2622 (93.9%)*	*169 (6.1%)*	*2791*
		Seronegative	*227 (21.2%)*	*845 (78.8%)*	*1072*
All subjects	*Predicted M0 PRNT90 Serostatus*	*Seropositive*	*2491 (95.3%)*	*122 (4.7%)*	*2613*
		Seronegative	*87 (6.9%)*	*1166 (93.1%)*	*1253*

*Adapted from pg 97 and 98 NS1 COS

The imputation is not perfect, 93.9% accurate for seropositives, and 78.8% for seronegatives with the PRNT50 method, while the PRNT 90 method is better with accuracy greater than 93% for both seropositives and seronegatives. Discussions with the statistical reviewer revealed the MI is sufficiently accurate to conduct efficacy and safety analyses within the context of the NS1 COS.

6.1.10 Study Population and Disposition

The study report does not describe the disposition from the original studies.

<u>Reviewer Comment:</u> From the original approval clinical review memo, assessment of population and subject disposition for CYD15, CYD14, and CYD23 did not identify any issues affecting interpretation of study results. Sex, age, and age subgroups were described as equally balanced, there was a high level of protocol compliance in Dengvaxia and placebo groups, and withdrawals due to serious adverse events (SAEs), adverse events (AEs), or loss to follow-up were minimal.

6.1.10.1 Populations Enrolled/Analyzed

This study did not enroll any new subjects, rather it is a post-hoc analysis of data from previous clinical trials. For both safety and efficacy analyses, the Full Analysis Set for Efficacy (FASE) from the source studies or subsets were utilized. The FASE comprised all subjects who received at least one injection of vaccine or placebo. For safety analyses, subjects were analyzed according to whether or not they actually received at least 1 injection of CYD dengue vaccine, while in efficacy analyses, subjects were analyzed according to the injection assigned at randomization (“as randomized” or intent-to-treat).

The Full Analysis Set for the SEP (FASSEP) was used for VE calculation during the SEP. The FASSEP is defined as the subjects who received at least one injection, who did not have severe non-compliance to GCP and who signed the SEP consent form.

In the sub-cohort, 1099 subjects (10.7% [1099/10,272]) were included from CYD14, 2130 subjects (10.2% [2130/20,854]) were included from CYD15, and 349 subjects (8.7% [349/3997]) were included from CYD23/57, and the percentage of subjects included from each group (CYD Dengue Vaccine or Placebo) was similar. See table 4 below, for a full description of subjects included in the close-out analysis.

Table 4: Number of subjects included in case-cohort analyses for different endpoints

Endpoints	Cases not in Sub-cohort n	Cases in Sub-cohort n	Non-cases in Sub-cohort n	All Cases n	All Sub-cohort n	All Subjects n
All dengue hospitalization occurring after M0	614	55	3523	669	3578	4192
CYD14	329	39	1060	368	1099	1428
CYD15	112	5	2125	117	2130	2242
CYD57	173	11	338	184	349	522
All severe dengue (IDMC) occurring after M0	131	16	3562	147	3578	3709
CYD14	92	14	1085	106	1099	1191
CYD15	25	1	2129	26	2130	2155
CYD57	14	1	348	15	349	363
All severe dengue (WHO 1997 Definition) occurring after M0	121	14	3564	135	3578	3699
CYD14	85	13	1086	98	1099	1184
CYD15	22	1	2129	23	2130	2152
CYD57	14	0	349	14	349	363
Symptomatic VCD occurring between M0 and end of Active Phase	1117	141	3088	1258	3229	4346
CYD14	525	71	1028	596	1099	1624
CYD15	592	70	2060	662	2130	2722
Symptomatic VCD occurring between M13 and end of Active Phase	579	75	2976	654	3051	3630
CYD14	204	34	1015	238	1049	1253
CYD15	375	41	1961	416	2002	2377
Symptomatic VCD occurring during SEP	400	36	2629	436	2665	3065
CYD14	330	30	981	360	1011	1341
CYD15	70	6	1648	76	1654	1724

n: number of subjects fulfilling the item listed; subjects with multiple cases were counted only once
*from pg 87 NS1 Close-out Study

Reviewer Comment: *The population analyzed in the NS1 COS was balanced and proportional, reflecting the populations included in the original clinical trials.*

6.1.10.1.1 Demographics

Table 4 below, illustrates demographic and baseline characteristics by treatment group for subjects in the sub-cohort were similar. Overall, 1869 subjects were female (52.2%), and 1709 subjects were male (47.8%) with a mean age of 10.9 years.

Table 5: Demographic and baseline characteristics by treatment group - subjects in the sub-cohort

		CYD Dengue Vaccine Group (N=2384)	Control Group (N=1194)	All (N=3578)
All Subjects	Sex: n (%)			
	M	2384	1194	3578
	Male	1122 (47.1)	587 (49.2)	1709 (47.8)
	Female	1262 (52.9)	607 (50.8)	1869 (52.2)
	Sex ratio: Male/Female	0.89	0.97	0.91
	Age (years)			
	M	2384	1194	3578
	Mean (SD)	10.9 (3.33)	10.9 (3.27)	10.9 (3.31)
	Min; Max	2.0; 17.0	2.1; 17.0	2.0; 17.0
	Median	11.3	11.1	11.3
	Q1; Q3	9.3; 13.3	9.2; 13.2	9.2; 13.3
	Age group: n (%)			
	M	2384	1194	3578
	<9 years	506 (21.2)	257 (21.5)	763 (21.3)
	>=9 years	1878 (78.8)	937 (78.5)	2815 (78.7)
	<6 years	263 (11.0)	126 (10.6)	389 (10.9)
	>=6 years	2121 (89.0)	1068 (89.4)	3189 (89.1)
	Weight (kg)			
	M	2211	1108	3319
	Mean (SD)	37.4 (14.8)	36.6 (14.6)	37.1 (14.7)
	Min; Max	9.0; 111	8.5; 102	8.5; 111
	Median	36.0	35.0	35.8
	Q1; Q3	27.1; 46.1	26.0; 45.1	27.0; 46.0
	Height (cm)			
	M	2211	1109	3320
	Mean (SD)	140 (19.0)	139 (19.1)	140 (19.1)
	Min; Max	75.0; 183	80.0; 180	75.0; 183

	Median	143	142	142
	Q1; Q3	131.0; 154	129; 153	130; 153
	BMI Body mass index (kg/m^2)			
	M	2211	1108	3319
	Mean (SD)	18.2 (3.83)	18.1 (3.72)	18.2 (3.79)
	Min; Max	6.6; 46.2	10.5; 38.8	6.6; 46.2
	Median	17.4	17.3	17.4
	Q1; Q3	15.6; 20.1	15.4; 19.9	15.5; 20.0

n: number of subjects fulfilling the item listed
N: total number of subjects selected in sub-cohort
Study group classified as treated (Subjects classified as CYD Dengue Vaccine Group if received at least 1 injection of CYD dengue vaccine)
SD: standard deviation
Q1; Q3: first quartile; third quartile
* from pg 80 NS1 Extension Report

Reviewer Comment:
Table 4 demonstrates that demographics and baseline characteristics were equally distributed between the vaccine and placebo group in the cohort for sex, age, weight, height, and BMI, which supports their suitability for comparisons in NS1 COS analyses

6.1.11 Efficacy Analyses

The NS1 Close-out study breaks down the analysis of VE by seropositive or seronegative status, age greater than or equal to 9 years of age, and less than 9 years old, and VE against any serotype, or specific serotypes.

Reviewer Comment:
The primary efficacy analysis of interest is the VE against any serotype in subjects 6 to 8 years old, and these are presented in section 7, the integrated overview of efficacy. These analyses were not highlighted in the NS1 Close-out report by the sponsor, but they were included in the clinical overview.

The forest plots summarizing the results in subjects designated as seronegative are presented here.

6.1.11.2 Analyses of Secondary Endpoints

The estimated efficacy against VCD during the Active Phase in subjects aged 6 to 8, 9 to 16, 2 to 5, and 6 to 16 years and classified as dengue seronegative is shown in Table 6 below. Estimates of VE ranged between 0.7 and 43.2% with all CI crossing zero except for PRNT90 estimates in the 9 to 16, and 6 to 16 year old age groups.

Table 6: VE against VCD due to any serotype during the whole Active Phase and PD3 (between Month 13 and end of Active Phase) in subjects aged 6 to 8 years, 9 to 16 years, 2 to 5 years, and 6 to 16 years classified as seronegative - NS1 Supplemental Analyses

Group of age	Method	Dengvaxia n (N)	Placebo n (N)	§	Vaccine Efficacy (95% CI)	
6-8 years CYD14	$PRNT_{50}$ M0 *	40.4 (43.8)	29.6 (26.2)		19.3	(-94.0, 66.4)
	$PRNT_{90}$ M0 †	47.1 (60.5)	38.8 (32.3)		37.0	(-15.0, 65.5)
	NS1 (Thr 9) M13‡	17 (42)	13 (27)		16.3	(-92.1, 63.5)
9 to 16 years CYD14+CYD15	$PRNT_{50}$ M0 *	190 (361.2)	149.5 (194.6)		33.4	(-10.1, 59.8)
	$PRNT_{90}$ M0 †	219 (447.9)	179.3 (215.1)		44.0	(24.6, 58.4)
	NS1 (Thr 9) M13‡	104 (309)	62 (157)		18.0	(-17.9, 43.0)
2 to 5 years CYD14	$PRNT_{50}$ M0 *	74.3 (95.9)	40.1 (48.4)		6.2	(-72.3, 48.9)
	$PRNT_{90}$ M0 †	92.2 (140.1)	54 (62.9)		23.7	(-20.9, 51.9)
	NS1 (Thr 9) M13‡	32 (86)	16 (46)		0.7	(-96.8, 49.9)
6 to 16 years CYD14+CYD15	$PRNT_{50}$ M0 *	230.4 (405)	179.1 (220.8)		31.8	(-9.9, 57.7)
	$PRNT_{90}$ M0 †	266.1 (508.4)	218.1 (247.4)		43.2	(25.4, 56.7)
	NS1 (Thr 9) M13‡	122 (353)	75 (184)		18.1	(-14.2, 41.3)

n represents the number of subjects fulfilling the item listed and N represents the total number of subjects selected in sub-cohort; For $PRNT_{50}$ M0 and $PRNT_{90}$ M0, n and N

are average numbers from 10 iterations of multiple imputations
For NS1(Thr9) M13 and NS1(Thr50) M13 classification, subjects with symptomatic VCD cases before M13 were excluded from the analyses Study group classified as randomized (subjects classified according to the injection assigned at randomization)
* Source: modified from 5.3.5.4 NS1 Close-out Report, Table 9.5.52, Table 9.5.55, Table 9.5.56, Table 9.5.57
† Source: modified from Table 1.4a
‡ Source: modified from 5.3.5.4 NS1 Extension Report, Table 9.229, Table 9.232, Table 9.233, and 5.3.5.4 NS1 Close-out Report, Table 9.5.9
§ Source: modified from Table 6a
from pg 7 response to 06 Oct 2022 IR

Reviewer Comment: *Dengvaxia is not approved for use in the seronegative, and the sponsor is not seeking this new indication. This analysis serves as a point of comparison with analyses in seropositive populations, and demonstrates the lower efficacy and broad CI observed in the NS1 inferral an imputation analyses involving seronegative populations when compared to seropositive populations.*

The findings in this table do not support efficacy of Dengvaxia in seronegatives in the 6 to 8 age group as efficacy estimates are low (less than 40) and all CI cross 0. In fact, analyses in this table in general do not support efficacy in seronegatives in general, as for all age groups VE estimates are low, with all except 2 CI crossing zero. This is consistent with findings in the seronegative population in the original review, which found VE in seronegative 9 to 16 year old individuals to be 44.5 with the 95%CI (-107.8, 85.1) crossing zero.

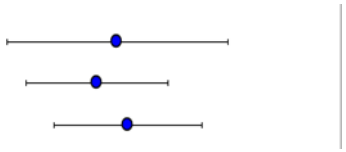
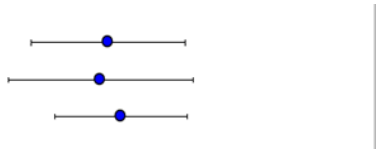
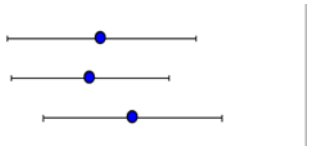
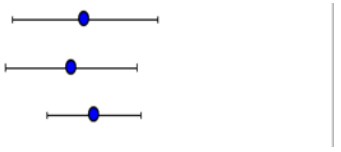
6.1.12 Safety Analyses

The NS1 Close-out study did not include a review of adverse events. Instead, this study focused its safety analysis on examining whether the increased risk of SVCD and HVCD, which was observed in the seronegative 9 to 16 year old age group as part of the original review, was also evident in other age groups. Again, the primary safety analysis of interest is amongst seropositive subjects 6 to 8 years old. The NS1 COS did not highlight these analyses, instead they were included in the clinical overview, and are presented in section 8, the integrated overview of safety.

6.1.12.4 Nonfatal Serious Adverse Events

The risk of HVCD and SVCD during the entire study period in subjects aged 6 to 8, 9 to 16, 2 to 5, and 6 to 16 years and classified as dengue seronegative is shown in Tables 7 and 8 below. Point estimates of risk of HVCD ranged between 1.180 and 2.646 with approximately half of analyses having CI above 1. Similarly, point estimates of risk of SVCD ranged between 2.054 and 6.734 with all CI crossing 1.

Table 7: Estimated risk of HVCD due to any serotypes during the Entire Study Period - subjects classified as seronegative, and who received at least 1 dose - Pooled Studies — NS1 Supplemental Analyses

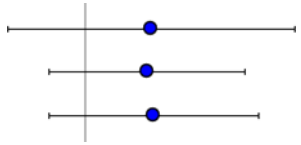
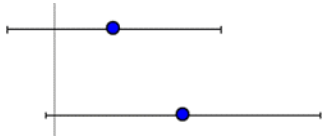
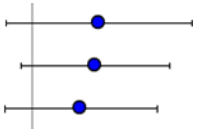
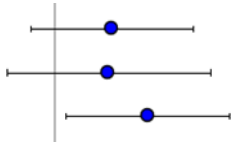
Group of age	Method	CYD Dengue Vaccine Group n (N)	Placebo Group n (N)	§	Risk of HVCD (95% CI)	
6 to 8 years CYD14+ CYD23/57	$PRNT_{50}$ M0 *	81 (78.8)	27.4 (46.5)		1.796	(0.766, 4.212)
	$PRNT_{90}$ M0 †	78 (78)	25 (48)		1.949	(1.101, 3.447)
	NS1 (Thr 9) M13‡	107.1 (115.6)	36.9 (60.6)		1.531	(0.886, 2.646)
9 to 16 years CYD14+ CYD23/57+ CYD15	$PRNT_{50}$ M0 *	71.8 (382.1)	30.9 (208)		1.258	(0.688, 2.299)
	$PRNT_{90}$ M0 †	59 (332)	22 (171)		1.385	(0.824, 2.326)
	NS1 (Thr 9) M13‡	94.6 (481.2)	39.5 (234.1)		1.180	(0.573, 2.432)
2 to 5 years CYD14+ CYD23/57	$PRNT_{50}$ M0 *	72.3 (116.5)	16.9 (55.4)		2.080	(1.001, 4.319)
	$PRNT_{90}$ M0 †	61 (104)	12 (53)		2.646	(1.323, 5.294)
	NS1 (Thr 9) M13‡	95.6 (169.1)	22.2 (73.3)		1.905	(1.033, 3.512)
6 to 16 years CYD14+ CYD23/57+ CYD15	$PRNT_{50}$ M0 *	152.8 (460.9)	58.3 (254.5)		1.456	(0.827, 2.564)
	$PRNT_{90}$ M0 †	137 (410)	47 (219)		1.568	(1.086, 2.264)
	NS1 (Thr 9) M13‡	201.7 (596.8)	76.4 (294.7)		1.309	(0.786, 2.181)

For all MI approaches, n represents the number of subjects fulfilling the item listed and N represents the total number of subjects selected in sub-cohort; n and N are average numbers from 10 iterations of multiple imputations. For both NS1 M13 approaches, n represents the number of subjects fulfilling the item listed and N represents the total

number of subjects selected in sub-cohort. Subjects with VCD cases before M13 were excluded from the analyses

Study group classified as treated (Subjects classified as CYD Dengue Vaccine Group if received at least 1 injection of CYD dengue vaccine)
* Source: modified from 5.3.5.4 NS1 Close-out Report, Table 9.2.118, Table 9.2.117, Table 9.2.116, Table 9.2.113
† Source: modified from Table 9.2.17a, Table 9.2.18a and 5.3.5.4 NS1 Close-out Report, Table 9.2.12, Table 9.2.9
‡ Source: modified from Table 1.8a
§ Source: modified from Table 10a
from pg 9 response to 06 Oct 2022 IR

Table 8: Estimated risk of SVCD due to any serotypes during the Entire Study Period - subjects aged 6 to 8 years, 9 to 16 years, 2 to 5 years, and 6 to 16 years, classified as seronegative, and who received at least 1 dose - Pooled Studies – NS1 Supplemental Analyses (from pg 10 IR response 2)

Group of age	Method	CYD Dengue Vaccine Group n (N)	Placebo Group n (N)	§	Risk of SVCD (95% CI)	
6 to 8 years CYD14+CYD23/57	MI $PRNT_{50}$ M0 *	11.2 (78.8)	2.8 (46.5)		2.650	(0.317, 22.138)
	MI $PRNT_{90}$ M0 †	14.7 (115.6)	3.2 (60.6)		2.483	(0.583, 10.567)
	NS1 (Thr 9) M13‡	9 (78)	2 (48)		2.752	(0.584, 12.968)
9 to 16 years CYD14+CYD23/57+ CYD15	MI $PRNT_{50}$ M0 *	15.6 (382.1)	3.8 (208)		2.413	(0.496, 11.748)
	MI $PRNT_{90}$ M0 †	20.7 (481.2)	5.4 (234.1)		N/A	N/A
	NS1 (Thr 9) M13‡	13 (332)	1 (171)		6.734	(0.878, 51.625)
2 to 5 years CYD14+CYD23/57	MI $PRNT_{50}$ M0 *	21.7 (116.5)	4 (55.4)		2.691	(0.673, 10.767)
	MI $PRNT_{90}$ M0 †	29.4 (169.1)	5.1 (73.3)		2.545	(0.844, 7.678)
	NS1 (Thr 9) M13‡	16 (104)	4 (53)		2.054	(0.658, 6.410)
6 to 16 years CYD14+CYD23/57+ CYD15	MI $PRNT_{50}$ M0 *	26.8 (460.9)	6.6 (254.5)		2.315	(0.700, 7.659)
	MI $PRNT_{90}$ M0 †	35.4 (596.8)	8.6 (294.7)		2.209	(0.491, 9.946)
	NS1 (Thr 9) M13‡	22 (410)	3 (219)		3.942	(1.171, 13.267)

For all MI approaches, n represents the number of subjects fulfilling the item listed and N represents the total number of subjects selected in sub-cohort; n and N are average numbers from 10 iterations of multiple imputations
For both NS1 M13 approaches, n represents the number of subjects fulfilling the item listed and N represents the total number of subjects selected in sub-cohort. Subjects with

VCD cases before M13 were excluded from the analyses
Study group classified as treated (Subjects classified as CYD Dengue Vaccine Group if received at least 1 injection of CYD dengue vaccine)
* Source: modified from 5.3.5.4 NS1 Close-out Report, Tables 9.3.71, Tables 9.3.74, Tables 9.3.75, Tables 9.3.76
† Source: modified from Table 1.2a
‡ Source: modified from Table 9.3.17a, Table 9.3.18a and 5.3.5.4 NS1 Close-out Report, Table 9.3.9, Table 9.3.12
§ Source: modified from Table 12a
from pg 10 response to 06 Oct 2022 IR

Reviewer Comment: Dengvaxia is not approved for use in the seronegative, and the sponsor is not seeking this new indication. These analyses serve as points of comparison with analyses in seropositive populations.

These findings demonstrate that the safety risks of increased rates of HVCD and SVCD observed in seronegative subjects 9 to 16 years in the original review, are also evident in seronegative individuals in the 6 to 8 age group too, as risk of HVCD varies between 1.531 and 1.949, and risk of SVCD varies between 2.483 and 2.752.

In fact, analyses in these tables demonstrate a risk for increased rates of HVCD and SVCD in general, amongst seronegative subjects in all the ages studied. This is consistent with findings in the seronegative population in the original review, which found an increased risk of severe dengue in seronegative subjects 9 to 16 years old of 6.25 with 95%CI (0.81, 48.32).

6.1.13 Study Summary and Conclusions

Please see sections 7.1.11 and 8.6, the conclusions for the integrated overview of efficacy and safety, respectively, as the key analyses from the NS1 COS are presented there.

7. INTEGRATED OVERVIEW OF EFFICACY

7.1 Indication #1

Dengvaxia (Dengue Tetravalent Vaccine, Live) or CYD is a vaccine indicated for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3, and 4. Dengvaxia is approved for use in individuals 6 through 16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas.

7.1.1 Methods of Integration

To support an extension of the age indication down to children 6 to 8 years of age, the integrated analyses of safety, immunogenicity, and efficacy have been updated with new long-term follow-up data from the 2 studies, CYD14 and CYD15. For integrated immunogenicity analyses, 6 studies included subjects aged 6 to 8 years of age and were thus considered (CYD14, CYD22, CYD23, CYD24, CYD28, and CYD32).

In addition, the extension of the age indication down to children 6 to 8 years of age is supported by the results of the NS1 Close-out study (NS1 COS), which is a pooled, post-hoc, case-cohort analysis of data from clinical trials evaluating the safety and efficacy of CYD dengue vaccine (CYD14, CYD15, and CYD23/CYD57).

Subjects in these studies received either CYD dengue vaccine or placebo, and the analysis of dengue outcomes were conducted according to dengue serostatus, which was performed from M0 or M13 onwards. Due to the limited number of baseline samples of study participants in the 3 efficacy studies, the Sponsor used a dengue anti- NS1 IgG ELISA to test samples collected at month 13 in all study participants. This assay allowed differentiating anti-NS1 antibodies induced by wild-type dengue infection from those induced by vaccination, as the CYD dengue vaccine contains genes encoding the NS1

from the yellow fever 17D vaccine virus rather than from dengue virus, so it could be used to infer participants' baseline dengue serostatus.

The dengue serostatus classification was performed using the following approaches:

- imputation
    - Measured or imputed plaque reduction neutralization test (PRNT50) at baseline (M0).
    - Measured or imputed PRNT90 at M0.
- Inferral:
    - Dengue anti-NS1 IgG ELISA assay readout at M13 (seronegativity defined as an anti-NS1 titer < 9 EU/mL and seropositivity as an anti-NS1 titer ≥ 9 EU/mL).
    - Strict seropositive classification (strict seropositivity defined as anti-NS1 titer ≥ 50 EU/mL at M13).

A case-cohort design (including all subjects with outcomes of interest and a randomly selected "sub-cohort") was used to obtain efficacy and risk estimates according to dengue serostatus.

VE performance against symptomatic VCD cases was calculated during the Active Phase and during the SEP, VE estimates were considered conclusive when the lower bound of the CI was above 0.

Reviewer Comment: The sponsor conducted the NS1 COS as serostatus at baseline was available in only approximately 3800 individuals, which did not adequately power analyses. Inferral methods, using the NS1 assay, and imputation methods, using statistical regression with NS1 as a continuous variable, and other variables such as age, sex, study arm, and occurrence of dengue, allowed the Sponsor to increase the number of subjects with a baseline serostatus designation available for analysis, and improve the precision of analyses. The NS1 COS contains many analyses, but the analyses most relevant to the proposed indication, are the analyses in seropositive subjects 6 to 8 years old. For VE the primary analysis, as in the original approval, is the VE for VCD from one month post dose 3 (M13) to the end of the active phase (M25). The most pertinent safety analyses are the risk of HVCD or SVCD until study end amongst seropositive 6 to 8 year old individuals.

7.1.2 Demographics and Baseline Characteristics

The demographic data among baseline seropositive subjects within each age group were similar between the CYD dengue vaccine Group and the Control Group in both the Full Analysis Set for Immunogenicity (FASI) and Full Analysis Set for Surveillance Expansion Period (FASSEP). Further, these populations remained comparable in terms of gender and mean age within each age group between study groups: male/female ratio was approximately 1 for all age groups, and the mean age was 7.5 years in subjects aged 6 to 8 years, slightly above 12 years in subjects aged 9 to 16 years, and slightly below 12 years in subjects aged 6 to 16 years. See table 9 for a breakdown of baseline demographics.

Table 9 Demographics at baseline – Seropositive subjects aged 6 to 8, 9 to 16 and 6 to 16 years – Efficacy analysis sets

		6-8 years				9-16 years				6-16 years			
Analysis Set	**Studies**	**CYD dengue vaccine Group (N=351)**		**Control Group (N=181)**		**CYD dengue vaccine Group (N=2027)**		**Control Group (N=1007)**		**CYD dengue vaccine Group (N=2380)**		**Control Group (N=1189)**	
FASI*		(n=236)		(n=126)		(n=1619)		(n=784)		(n=1855		(n=910)	
		Male n (%)	**Mean Age**	**Male n (%)**	**Mean Age**	**Male n (%)**	**Mean Age**	**Male n (%)**	**Mean Age**	**Male n (%)**	**Mean Age**	**Male n (%)**	**Mean Age**
	CYD14	82 (48.5)	7.5	46 (52.3)	7.4	245 (50.3)	12.3	122 (48.6)	12.2	327 (49.8)	11.1	168 (49.6)	11.0
	CYD15					512 (47.7)	12.4	272 (53.1)	12.5	512 (47.7)	12.4	272 (53.1)	12.5
	CYD14+CYD15					757 (48.5)	12.4	394 (51.6)	12.4	839 (48.5)	11.9	440 (51.7)	11.9
	CYD23	27 (40.3)	7.7	17 (44.7)	7.7	28 (47.5)	10.0	8 (38.1)	10.2	55 (43.7)	8.8	25 (42.4)	8.6
	CYD14+CYD15+CYD23	109 (46.2)	7.5	63 (50.0)	7.5	785 (48.5)	12.3	402 (51.3)	12.4	894 (48.2)	11.7	465 (51.1)	11.7
FASSEP†		(n=167)		(n=85)		(n=1335)		(n=653)		(n=1502)		(n=738)	
		Male n (%)	**Mean Age**	**Male n (%)**	**Mean Age**	**Male n (%)**	**Mean Age**	**Male n (%)**	**Mean Age**	**Male n (%)**	**Mean Age**	**Male n (%)**	**Mean Age**
	CYD14	81 (48.5)	7.5	45 (52.9)	7.4	228 (50.6)	12.3	115 (48.1)	12.2	309 (50.0)	11.0	160 (49.4)	11.0
	CYD15					411 (46.5)	12.4	221 (53.4)	12.5	411 (46.5)	12.4	221 (53.4)	12.5
	CYD14+CYD15					639 (47.9)	12.3	336 (51.5)	12.4	720 (47.9)	11.8	381 (51.6)	11.8

N: number of subjects in the immunogenicity subset n: number of subjects fulfilling the item listed
Mean age (years)
* Source: Modified from 5.3.5.3 Integrated Efficacy Analysis Report, Table 3.6.5.39, Table 3.6.6.3, Table 3.6.7.39, Table 3.6.8.2, Table 3.6.8.39
† Source: Modified from 5.3.5.3 Integrated Efficacy Analysis Report, Table 3.6.5.39, Table 3.6.5.43, Table 3.6.7.27, Table 3.6.7.39, Table 3.6.8.2, Table 3.6.8.25 from pg 55 of SCE

Mean age of subjects among the different age groups was similar between the CYD dengue vaccine and the Control Groups in subjects aged 2 to 5 years, as mean age was between 3.26 and 4.57 years in the CYD dengue vaccine Group and between 3.19 and 4.89 years in the Control Group. Cumulatively by region, the sex ratio was comparable, 44.3% male in the vaccine group vs. 50.7% male in the control group in the Asia Pacific, and 56.4% male in the vaccine group vs. 52.4% male in the control group in Latin America. See table 10 for a breakdown of baseline demographics.

Table 10: Demographics at baseline – Seropositive subjects aged 2 to 5 years - FAS and FASI

		CYD dengue vaccine Group			Control Group		
Region	**Study**	**N**	**Male n (%)**	**Mean Age (yrs)**	**N**	**Male n (%)**	**Mean Age (yrs)**
Endemic AP	**CYD14**	243	110 (45.3)	3.72	105	46 (43.8)	4.01
	CYD22	24	10 (41.7)	3.83	12	8 (66.7)	3.92
	CYD23	14	5 (35.7)	4.57	9	7 (77.8)	4.89
	CYD28	9	3 (33.3)	3.33	4	2 (50.0)	4.00
	CYD32	44	20 (45.5)	3.64	12	9 (75.0)	3.67
	All	334	148 (44.3)	3.74	142	72 (50.7)	4.03
Endemic LatAm	**CYD24**	39	22 (56.4)	3.26	21	11 (52.4)	3.19
	All	39	22 (56.4)	3.26	21	11 (52.4)	3.19

n: number of subjects fulfilling the item listed

from pg 32 of SCE

Ethnicity was collected in all studies, except for CYD22, CYD23, CYD24, CYD28, CYD67, and CYD71. In AP endemic regions, almost 90% of subjects were of Asian origin (both study groups). In Latin America endemic regions, most subjects were of Hispanic origin, of mixed ethnic origin, or reported as “other.”

A total of 16,319 subjects completed long-term follow-up (Year 6, corresponding to the 4th year of long-term follow-up).

Reviewer Comment: No new clinical studies were completed for this age-lowering supplement, as the sponsor is utilizing a post-hoc analysis of previously conducted clinical trials from the original approval to support age-lowering. From the original approval clinical review memo, assessment of population and subject disposition for CYD15, CYD14, and CYD23 did not identify any issues affecting interpretation of study results. Sex, age, and age subgroups were described as equally balanced, and there was a high level of protocol compliance in Dengvaxia and placebo groups, with withdrawals due to SAEs, AEs, or loss to follow-up being minimal.

7.1.4 Analysis of Primary Endpoint(s)

Table 10 summarizes the NS1 analyses. In addition to the analysis in 6 to 8 year old seropositive subjects, analyses in seropositive 9 to 16, and 2 to 5 year old age groups serve as comparators. Finally, VE is presented in seropositive subjects aged 6 to 16

years to provide a comprehensive view of efficacy.

VE estimates against symptomatic VCD cases in seropositive subjects aged 6 to 8 years, were conclusive and comparable for the 4 approaches, as VE ranged between 55.8 and 67.3. In comparison, VE estimates in older children aged 9 to 16 years tended to be higher at approximately 78%. In younger subjects aged 2 to 5 years, VE estimates tended to be lower for the PRNT approaches, but a little higher for the NS1 methods compared to the 6 to 8 age group.

In subjects aged 6 to 16 years (CYD14+CYD15), VE estimates against symptomatic VCD cases were around 76%, and were conclusive and consistent for the 4 approaches.

Table 11: VE against VCD due to any serotype during the whole Active Phase and PD3 in subjects aged 6 to 8 years, 9 to 16 years, 2 to 5 years, and 6 to 16 years classified as seropositive - NS1 Supplemental Analyses

Group of age	Method	Dengvaxia n (N)	Placebo n (N)	Vaccine Efficacy (95% CI)	
6-8 years CYD14	MI $PRNT_{50}$ M0 *	35.6 (99.2)	55.4 (51.8)	67.3	(39.9, 82.2)
	MI $PRNT_{90}$ M0 †	28.9 (82.5)	46.2 (45.7)	66.3	(38.3, 81.6)
	NS1 (Thr 9) M13‡	14 (90)	15 (44)	55.8	(1.8, 80.1)
	NS1 (Thr 50) M13 §	12 (76)	13 (34)	60.5	(6.2, 83.4)
9 to 16 years CYD14+ CYD15	MI $PRNT_{50}$ M0 *	177 (1433.8)	371.5 (696.4)	77.6	(70.2, 83.2)
	MI $PRNT_{90}$ M0 †	148 (1347.1)	341.7 (675.9)	79.0	(73.3, 83.5)
	NS1 (Thr 9) M13‡	111 (1389)	222 (656)	76.7	(70.2, 81.7)
	NS1 (Thr 50) M13 §	79 (1249)	160 (565)	77.9	(70.6, 83.4)
2 to 5 years CYD14	MI $PRNT_{50}$ M0 *	45.7 (120.1)	48.9 (57.6)	57.1	(21.6, 76.5)
	MI $PRNT_{90}$ M0 †	27.8 (75.9)	35 (43.1)	57.2	(19.0, 77.4)
	NS1 (Thr 9) M13‡	16 (119)	27 (47)	77.1	(54.6, 88.4)
	NS1 (Thr 50) M13 §	7 (72)	12 (35)	74.0	(31.6, 90.1)
6 to 16 years CYD14+CYD15	MI $PRNT_{50}$ M0 *	212.6 (1533)	426.9 (748.2)	76.5	(69.1, 82.2)
	MI $PRNT_{90}$ M0 †	176.9 (1429.6)	387.9 (721.6)	77.7	(72.1, 82.2)
	NS1 (Thr 9) M13‡	125 (1492)	237 (700)	75.6	(69.2, 80.6)
	NS1 (Thr 50) M13 §	91 (1325)	173 (599)	76.5	(69.3, 82.1)

n represents the number of subjects fulfilling the item listed and N represents the total number of subjects selected in sub-cohort; For MI PRNT50 M0 and MI PRNT90 M0, n and N are average numbers from 10 iterations of multiple imputations
For NS1(Thr9) M13 and NS1(Thr50) M13 classification, subjects with symptomatic VCD cases before M13 were excluded from the analyses Study group classified as randomized (subjects classified according to the injection assigned at randomization)
* Source: modified from 5.3.5.4 NS1 Close-out Report, Table 9.5.60, Table 9.5.63, Table 9.5.64, and Table 9.5.65
† Source: modified from 5.3.5.4 NS1 Close-out Report, Appendix 15, Table 2.8, and 5.3.5.4 NS1 additional outputs, Table 1.4
‡ Source: modified from 5.3.5.4 NS1 Extension Report, Table 9.236, Table 9.239, and Table 9.240, and 5.3.5.4 NS1 Close-out Report, Table 9.5.10
§ Source: modified from 5.3.5.4 NS1 Close-out Report, Table 9.5.19, Table 9.5.15, Table 9.5.18, and Table 9.5.20
from pg 27 of CO

Reviewer Comment: The VE in the 6 to 8 year old group ranges from 55.8 to 67.3 and the LBCI for the imputations are greater than 25%, while the LBCI for the NS1 inferral approaches are 1.8 and 6.2. The point estimates and the CIs are acceptable and show efficacy as this post-hoc analysis did not prespecify a LBCI >25% and was not powered to exceed this threshold.
The VE estimates for 9 to 16 range from 76.7 to 79.0 and CIs are small with the LBCI greater than 25%. This is similar to the finding in the original approval of a VE of 80.6 95%CI (50.7; 93.2) in seropositive individuals 9 to 16 years old, and the consistency supports the validity of these analyses.
Findings for the combined 6 to 16 year old group are similar, ranging between and 75.6. and 77.7 with LBCI >25%, which is reassuring, as efficacy is shown to be adequate for the whole age range proposed by the sponsor's new indication.

7.1.5 Analysis of Secondary Endpoint(s)

Immunogenicity Results

Tables 1.9 and 1.10 contain data showing an increase in GMTs for each of the 4 serotypes after 3 injections of the CYD dengue vaccine in baseline seropositive subjects in both the 6 to 8 years and 9 to 17 year old age groups. In general, a trend toward higher post dose 3 (PD3) GMT levels was observed in subjects with higher baseline titers in all age groups. PD3/baseline geometric mean of titer ratio (GMTRs) in the 6 to 8 year old age group ranged from approximately 2 to 9, depending on the study and serotype considered, while in 9 to 17 year old individuals, GMTR were narrower ranging from 3 to 4.

Table 12: Geometric means of Dengue $PRNT_{50}$ antibody (1/dil) pre-Dose 1 and PD3 for each serotype, in seropositive subjects aged 6 to 8 years, and 9 to 17 years

			Serotype 1		Serotype 2		Serotype 3		Serotype 4	
Age group	Study	N	Pre-dose 1 GM (M) (95% CI)	Post-dose 3 GM (M) (95% CI)	Pre-dose 1 GM (M) (95% CI)	Post-dose 3 GM (M) (95% CI)	Pre-dose 1 GM (M) (95% CI)	Post-dose 3 GM (M) (95% CI)	Pre-dose 1 GM (M) (95% CI)	Post-dose 3 GM (M) (95% CI)
6-8 years	CYD14	168	**80.8** (167)	**203** (166)	**118** (168)	**369** (166)	**105** (168)	**316** (166)	**48.4** (168)	**175** (166)
			(57.3; 114)	(154; 268)	(86.0; 161)	(298; 457)	(75.5; 145)	(244; 411)	(37.2; 63.0)	(145; 211)
	CYD23	66	**66.5** (66)	**213** (63)	**118** (66)	**548** (63)	**49.5** (66)	**462** (63)	**53.8** (66)	**195** (63)
			(39.4; 112)	(138; 329)	(69.0; 202)	(355; 844)	(34.8; 70.5)	(328; 651)	(35.2; 82.2)	(141; 269)
9-17 years	CYD14	485	**167** (481)	**437** (482)	**319** (482)	**793** (481)	**160** (477)	**443** (481)	**83.8** (483)	**272** (481)
			(138; 202)	(373; 511)	(274; 373)	(704; 892)	(135; 190)	(387; 507)	(72.0; 97.6)	(245; 302)
	CYD15	1048	**278** (1046)	**703** (1040)	**306** (1048)	**860** (1040)	**261** (1048)	**762** (1040)	**73.3** (1046)	**306** (1040)
			(247; 313)	(634; 781)	(277; 338)	(796; 930)	(235; 289)	(699; 830)	(66.6; 80.7)	(286; 328)

M: number of subjects with available Ab titer for the relevant endpoint
Adapted from pg 34 and 36 of SCE

Reviewer Comment:
The increase in GMT post dose 3 in 6 to 8 year old individuals are similar to those observed in 9 to 17 year old seropositive subjects. Although the increase in post-dose 3 GMT for 6 to 8 year old individuals ranged from 2 to 9 fold increases, for most serotypes and comparisons the increase was similar for both age groups with increases of 3 to 4 times the baseline geometric mean. The absolute value of the post dose 3 GMT in the 9 to 17 year old group were higher however, 300 to 800 compared to 200 to 500 in 6 to 8 year old individuals.

A similar pattern was observed in the original clinical trial data. From the original approval clinical review memo: In study CYD 15, immunogenicity data supported the conclusion that Dengvaxia vaccine was immunogenic for each serotype. 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 (so also consistent with the 2 to 9 fold increase observed among seropositive 6 to 8 year old individuals). In the control group, as expected, there was no increase in GMTs following placebo doses. These original analyses included subjects who were dengue seropositive and dengue seronegative at baseline.

In addition, although no correlate of protection has been identified for Dengvaxia, the original submission identified a pattern of higher GMTs being protective, as seen in table 13 below.

Table 13: Summary of GMTs of dengue antibodies against each serotype with the parental dengue virus strains for dengue cases post-Dose 3 and non-cases - Dengue PRNT assay – mFASE

	CYD Dengue Vaccine Group (N=6772)						Control Group (N=3379)					
Post-Inj (V06)	**Cases**			**Non cases**			**Cases**			**Non cases**		
Strain	**n**	**GMT**	**(95% CI)**	**n**	**GMT**	**(95% CI)**	**n**	**GMT**	**(95% CI)**	**n**	**GMT**	**(95% CI)**
Dengue Virus Serotype 1 (PRNT-[l/dil])	50	**58.1**	(41.9; 80.4)	1275	**167**	(150; 185)	47	**11.8**	(8.07; 17.2)	604	**44.7**	(36.8; 54.3)
Dengue Virus Serotype 2 (PRNT-[l/dil])	36	**129**	(92.5; 179)	1273	**352**	(324; 382)	26	**23.8**	(12.6; 45.0)	604	**61.8**	(51.3; 74.6)
Dengue Virus Serotype 3 (PRNT-[l/dil])	10	**77.5**	(49.6; 121)	1273	**208**	(190; 228)	23	**22.7**	(14.0; 36.6)	604	**40.0**	(33.8; 47.3)
Dengue Virus Serotype 4 (PRNT-[l/dil])	17	**61.7**	(32.9; 116)	1274	**150**	(140; 161)	34	**13.7**	(8.85; 21.1)	604	**24.3**	(21.1; 28.0)

n: 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 V01 and the end of the Active Phase. Source: Section 10, Table 10.194 from pg 345 original BLA CYD 14 study report

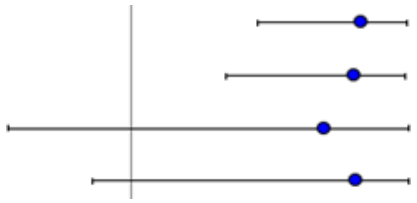
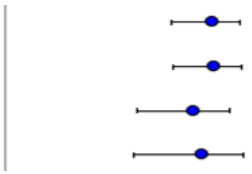
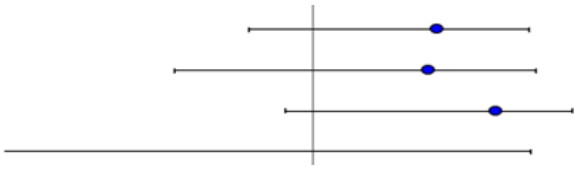
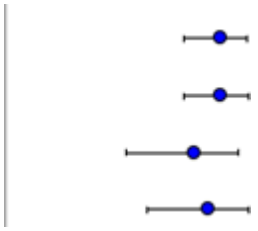
Table 13 shows that higher GMTs tend to be protective, as individuals who were likely protected (non-cases amongst vaccinees) had 2 to 3 fold higher GMTs than cases (ranging from 150 to 352 in non-cases vs 58 to 129 amongst cases). The GMTs in the placebo group were even lower than amongst the vaccinees (11.8 to 23.8 in cases vs 24.3 to 61.8 amongst non-cases).

These data demonstrates that immunogenicity in the 6 to 8 year old seropositive age group is both similar to that observed in 9 to 17 year old individuals during the original clinical review, and the increase specifically observed in seropositive 9 to 17 year old individuals, while data comparing cases to non-cases indicate higher GMTs tend to be protective. These similarities support Dengvaxia being immunogenic and protective in the seropositive 6 to 8 year old age group.

7.1.6 Other Endpoints

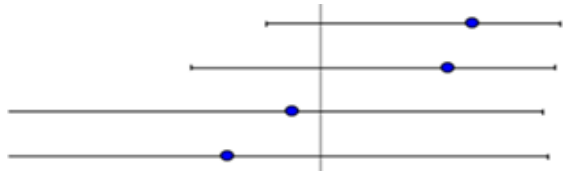
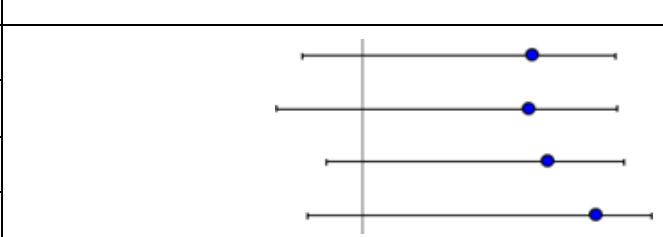
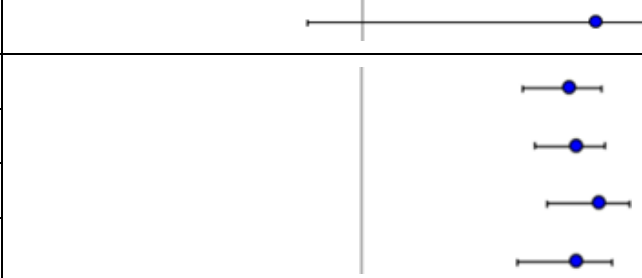
Tables 14, 15, 16, and 17 below, are from the sponsor's response to the IR dated 06 Oct 2022. The tables are forest plots showing VE against VCD for each serotype. VE Point estimates in seropositive 6 to 8 year old individuals for serotypes 1, 3, and 4 vary from 63.1 to 86.0 and are better than for serotype 2, which has point estimates for the imputational approach in the 40s. In general, the CIs are broad, with many crossing zero. The point estimates for seropositive subjects in the 9 to 16 year age group and in the combined 6 to 16 year age group, however, are better and vary from 60 to 90%, with narrow CIs that have LBCIs >25%.

Table 14: VE against VCD due to serotype 1 during the whole Active Phase and PD3 (between Month 13 and end of Active Phase) in subjects aged 6 to 8 years, 9 to 16 years, 2 to 5 years, and 6 to 16 years classified as seropositive - NS1 Supplemental Analyses

Group of age	Method	Dengvaxia n (N)	Placebo n (N)	**	Vaccine Efficacy (95% CI)	
6-8 years CYD14	$PRNT_{50}$ M0 *	11 (99.2)	23.3 (51.8)		75.4	(41.4, 89.7)
	$PRNT_{90}$ M0 †	9.5 (82.5)	19.3 (45.7)		72.7	(31.2, 89.1)
	NS1 (Thr 9) M13‡	4 (93)	5 (44)		63.1	(-38.8, 90.2)
	NS1 (Thr 50) M13 §	3 (76)	5 (34)		73.7	(-11.8, 93.8)
9 to 16 years CYD14+ CYD15	$PRNT_{50}$ M0 *	65.1 (1433.8)	102.5 (696.4)		69.4	(56.0, 78.7)
	$PRNT_{90}$ M0 †	56.5 (1347.1)	93.5 (675.9)		70.0	(56.6, 79.2)
	NS1 (Thr 9) M13‡	44 (1399)	56 (656)		63.1	(44.7, 75.4)
	NS1 (Thr 50) M13 §	27 (1249)	36 (565)		65.9	(43.4, 79.5)
2 to 5 years CYD14	$PRNT_{50}$ M0 *	25.4 (120.1)	20.3 (57.6)		41.6	(-20.1, 71.6)
	$PRNT_{90}$ M0 †	16.4 (75.9)	14.7 (43.1)		38.9	(-44.8, 74.2)
	NS1 (Thr 9) M13‡	8 (120)	8 (47)		60.7	(-8.4, 85.7)
	NS1 (Thr 50) M13 §	5 (72)	1 (35)		-133.1	(-1870.4, 72.4)
6 to 16 years CYD14+CYD15	$PRNT_{50}$ M0 *	76.1 (1533)	125.8 (748.2)		70.7	(58.6, 79.3)
	$PRNT_{90}$ M0 †	66 (1429.6)	112.8 (721.6)		70.7	(58.5, 79.4)
	NS1 (Thr 9) M13‡	48 (1492)	61 (700)		63.1	(45.6, 75.0)
	NS1 (Thr 50) M13 §	30 (1325)	41 (599)		66.9	(46.5, 79.5)

n represents the number of subjects fulfilling the item listed and N represents the total number of subjects selected in sub-cohort; For PRNT50 M0 and PRNT90 M0, n and N are average numbers from 10 iterations of multiple imputations
For NS1(Thr9) M13 and NS1(Thr50) M13 classification, subjects with symptomatic VCD cases before M13 were excluded from the analyses Study group classified as randomized (subjects classified according to the injection assigned at randomization)
*Source: modified from 5.3.5.4 NS1 Close-out Report, Table 9.5.76, Table 9.5.79, Table 9.5.80, Table 9.5.81
† Source: modified from 5.3.5.4 NS1 additional outputs Table 1.5
‡ Source: modified from 5.3.5.4 NS1 Close-out Report, Table 9.5.37, Table 9.5.32, Table 9.5.36, Table 9.5.35
§ Source: modified from 5.3.5.4 NS1 Close-out Report, Table 9.5.48, Table 9.5.44, Table 9.5.47, Table 9.5.49
** Source: modified from Table 6b
from pg 14 response to 06 Oct 2022 IR

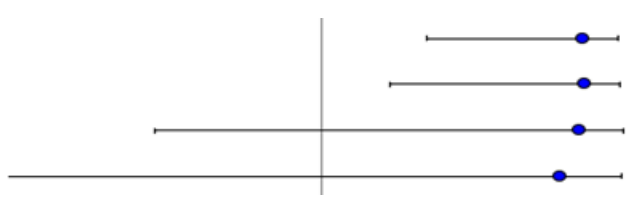
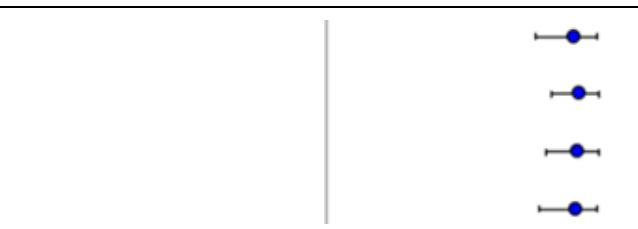
Table 15: VE against VCD due to serotype 2 during the whole Active Phase and PD3 (between Month 13 and end of Active Phase) in subjects aged 6 to 8 years, 9 to 16 years, 2 to 5 years, and 6 to 16 years classified as seropositive - NS1 Supplemental Analyses

Group of age	Method	Dengvaxia n (N)	Placebo n (N)	**	Vaccine Efficacy (95% CI)	
6-8 years CYD14	$PRNT_{50}$ M0 *	15.9 (99.2)	16.3 (51.8)		49.9	(-16.7, 78.5)
	$PRNT_{90}$ M0 †	13.8 (82.5)	13 (45.7)		42.5	(-40.9, 76.6)
	NS1 (Thr 9) M13‡	7 (93)	3 (44)		-8.5	(-330.2, 72.7)
	NS1 (Thr 50) M13 §	6 (76)	2 (34)		-29.5	(-556.3, 74.5)
9 to 16 years CYD14+ CYD15	$PRNT_{50}$ M0 *	50.3 (1433.8)	83.9 (696.4)		71.3	(55.3, 81.6)
	$PRNT_{90}$ M0 †	38.1 (1347.1)	74.6 (675.9)		74.7	(60.5, 83.7)
	NS1 (Thr 9) M13‡	25 (1399)	43 (656)		72.7	(55.0, 83.4)
	NS1 (Thr 50) M13 §	20 (1249)	38 (565)		76.2	(58.8, 86.2)
2 to 5 years CYD14	$PRNT_{50}$ M0 *	11.8 (120.1)	12.9 (57.6)		56.9	(-19.1, 84.4)
	$PRNT_{90}$ M0 †	7.6 (75.9)	9.8 (43.1)		56.0	(-27.6, 84.9)
	NS1 (Thr 9) M13‡	7 (120)	7 (47)		62.0	(-10.8, 87.0)
	NS1 (Thr 50) M13 §	2 (72)	4 (35)		78.1	(-17.5, 95.9)
6 to 16 years CYD14+CYD15	$PRNT_{50}$ M0 *	66.2 (1533)	100.2 (748.2)		68.2	(53.1, 78.4)
	$PRNT_{90}$ M0 †	51.9 (1429.6)	87.6 (721.6)		70.4	(56.7, 79.7)
	NS1 (Thr 9) M13‡	32 (1492)	46 (700)		67.3	(48.4, 79.4)
	NS1 (Thr 50) M13 §	26 (1325)	40 (599)		70.6	(51.5, 82.2)

n represents the number of subjects fulfilling the item listed and N represents the total number of subjects selected in sub-cohort; For PRNT50 M0 and PRNT90 M0, n and N are average numbers from 10 iterations of multiple imputations

For NS1(Thr9) M13 and NS1(Thr50) M13 classification, subjects with symptomatic VCD cases before M13 were excluded from the analyses Study group classified as randomized (subjects classified according to the injection assigned at randomization)
*Source: modified from 5.3.5.4 NS1 Close-out Report, Table 9.5.76, Table 9.5.79, Table 9.5.80, Table 9.5.81
† Source: modified from 5.3.5.4 NS1 additional outputs Table 1.5
‡ Source: modified from 5.3.5.4 NS1 Close-out Report, Table 9.5.37, Table 9.5.32, Table 9.5.36, Table 9.5.35
§ Source: modified from 5.3.5.4 NS1 Close-out Report, Table 9.5.48, Table 9.5.44, Table 9.5.47, Table 9.5.49
** Source: modified from Table 6b
from pg 15-16 response to 06 Oct 2022 IR

Table 16: VE against VCD due to serotype 3 during the whole Active Phase and PD3 (between Month 13 and end of Active Phase) in subjects aged 6 to 8 years, 9 to 16 years, 2 to 5 years, and 6 to 16 years classified as seropositive - NS1 Supplemental Analyses

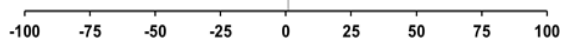
Group of age	Method	Dengvaxia n (N)	Placebo n (N)	**	Vaccine Efficacy (95% CI)	
6-8 years CYD14	$PRNT_{50}$ M0 *	2.6 (99.2)	9.2 (51.8)		85.8	(34.6, 96.9)
	$PRNT_{90}$ M0 †	2.3 (82.5)	8.6 (45.7)		86.0	(23.0, 97.5)
	NS1 (Thr 9) M13‡	1 (93)	3 (44)		84.1	(-53.3, 98.4)
	NS1 (Thr 50) M13 §	1 (76)	2 (34)		77.7	(-146.8, 98.0)
9 to 16 years CYD14+ CYD15	$PRNT_{50}$ M0 *	39.1 (1433.8)	95.3 (696.4)		80.3	(67.0, 88.3)
	$PRNT_{90}$ M0 †	33.4 (1347.1)	93.1 (675.9)		82.2	(72.6, 88.4)
	NS1 (Thr 9) M13‡	29 (1399)	78 (656)		82.7	(73.3, 88.8)
	NS1 (Thr 50) M13 §	23 (1249)	55 (565)		81.2	(69.2, 88.5)
2 to 5 years CYD14	$PRNT_{50}$ M0 *	5.1 (120.1)	7.2 (57.6)		66.3	(-25.6, 91.0)
	$PRNT_{90}$ M0 †	3 (75.9)	5.3 (43.1)		68.1	(-52.0, 93.3)
	NS1 (Thr 9) M13‡	0 (120)	5 (47)		N/A	N/A
	NS1 (Thr 50) M13 §	0 (72)	4 (35)		N/A	N/A
6 to 16 years CYD14+CYD15	$PRNT_{50}$ M0 *	41.7 (1533)	104.5 (748.2)		80.8	(68.3, 88.4)
	$PRNT_{90}$ M0 †	35.7 (1429.6)	101.7 (721.6)		82.5	(73.3, 88.6)
	NS1 (Thr 9) M13‡	30 (1492)	81 (700)		82.7	(73.6, 88.7)
	NS1 (Thr 50) M13 §	24 (1325)	57 (599)		81.1	(69.3, 88.4)

n represents the number of subjects fulfilling the item listed and N represents the total number of subjects selected in sub-cohort; For PRNT50 M0 and PRNT90 M0, n and N are average numbers from 10 iterations of multiple imputations

For NS1(Thr9) M13 and NS1(Thr50) M13 classification, subjects with symptomatic VCD cases before M13 were excluded from the analyses Study group classified as randomized (subjects classified according to the injection assigned at randomization)
*Source: modified from 5.3.5.4 NS1 Close-out Report, Table 9.5.76, Table 9.5.79, Table 9.5.80, Table 9.5.81
† Source: modified from 5.3.5.4 NS1 additional outputs Table 1.5
‡ Source: modified from 5.3.5.4 NS1 Close-out Report, Table 9.5.37, Table 9.5.32, Table 9.5.36, Table 9.5.35
§ Source: modified from 5.3.5.4 NS1 Close-out Report, Table 9.5.48, Table 9.5.44, Table 9.5.47, Table 9.5.49
** Source: modified from Table 6b
from pg 17-18 response to 06 Oct 2022 IR

Table 17: VE against VCD due to serotype 4 during the whole Active Phase and PD3 (between Month 13 and end of Active Phase) in subjects aged 6 to 8 years, 9 to 16 years, 2 to 5 years, and 6 to 16 years classified as seropositive - NS1 Supplemental Analyses

Group of age	Method	Dengvaxia n (N)	Placebo n (N)	**	Vaccine Efficacy (95% CI)	
6-8 years CYD14	$PRNT_{50}$ M0 *	5.8 (99.2)	8.6 (51.8)		64.7	(-11.4, 88.8)
	$PRNT_{90}$ M0 †	3.2 (82.5)	7.2 (45.7)		75.8	(-0.6, 94.2)
	NS1 (Thr 9) M13‡	2 (93)	4 (44)		76.6	(-29.2, 95.8)
	NS1 (Thr 50) M13 §	2 (76)	4 (34)		78.3	(-20.0, 96.1)
9 to 16 years CYD14+ CYD15	$PRNT_{50}$ M0 *	19.2 (1433.8)	93.1 (696.4)		90.4	(80.2, 95.3)
	$PRNT_{90}$ M0 †	16.3 (1347.1)	83.5 (675.9)		90.4	(82.3, 94.8)
	NS1 (Thr 9) M13‡	10 (1399)	48 (656)		90.4	(80.9, 95.1)
	NS1 (Thr 50) M13 §	8 (1249)	33 (565)		89.2	(76.5, 95.0)
2 to 5 years CYD14	$PRNT_{50}$ M0 *	3.5 (120.1)	10.9 (57.6)		85.7	(26.1, 97.2)
	$PRNT_{90}$ M0 †	0.8 (75.9)	7.2 (43.1)		N/A	N/A
	NS1 (Thr 9) M13‡	1 (120)	7 (47)		94.2	(52.7, 99.3)
	NS1 (Thr 50) M13 §	0 (72)	1 (35)		N/A	N/A
6 to 16 years CYD14+CYD15	$PRNT_{50}$ M0 *	25 (1533)	101.7 (748.2)		88.4	(78.5, 93.7)
	$PRNT_{90}$ M0 †	19.5 (1429.6)	90.7 (721.6)		89.4	(81.4, 93.9)
	NS1 (Thr 9) M13‡	12 (1492)	52 (700)		89.3	(79.9, 94.3)
	NS1 (Thr 50) M13 §	10 (1325)	37 (599)		87.9	(75.7, 94.0)



n represents the number of subjects fulfilling the item listed and N represents the total number of subjects selected in sub-cohort; For PRNT50 M0 and PRNT90 M0, n and N are average numbers from 10 iterations of multiple imputations
For NS1(Thr9) M13 and NS1(Thr50) M13 classification, subjects with symptomatic VCD cases before M13 were excluded from the analyses
Study group classified as randomized (subjects classified according to the injection assigned at randomization)
*Source: modified from 5.3.5.4 NS1 Close-out Report, Table 9.5.76, Table 9.5.79, Table 9.5.80, Table 9.5.81
† Source: modified from 5.3.5.4 NS1 additional outputs Table 1.5
‡ Source: modified from 5.3.5.4 NS1 Close-out Report, Table 9.5.37, Table 9.5.32, Table 9.5.36, Table 9.5.35
§ Source: modified from 5.3.5.4 NS1 Close-out Report, Table 9.5.48, Table 9.5.44, Table 9.5.47, Table 9.5.49

** Source: modified from Table 6b
from pg 19-20 response to 06 Oct 2022 IR

Reviewer Comment:
These results are similar to the VE against each serotype from the original approval, with better efficacy against serotypes 3 and 4, and lower efficacy against serotype 2. In addition, as in the original approval, this analysis and the studies were not meant to be powered to evaluate serotype-specific VE, so the broad CIs can be attributed to a small number of cases identified.

The negative VE estimates for 6 to 8 year old individuals for serotype 2 in the analyses using the inferral method (NS1) appear to be outliers, as the MI methods had positive estimates of VE (49.9% and 42.5%), which are more consistent with the previous estimates for VE against serotype 2 in the original CYD15 study (42.5%). These are also more consistent with the results for the pooled analyses for ages 6 to 16 years of age, as all methods had positive VE point estimates with LBCI > 25%. This suggests the negative inferral VE point estimates and the corresponding large CIs for serotype 2 in 6 to 8 year old individuals are due to the small number of cases involved.

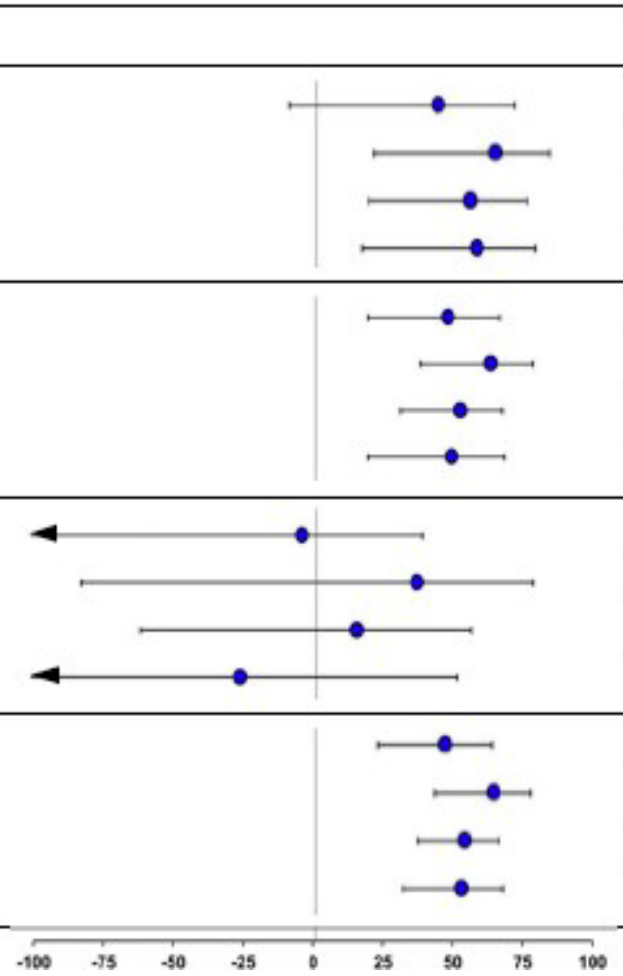
Although the studies and analyses are not powered to evaluate efficacy for each serotype, it is reassuring that the estimate of VE in the combined 6 to 16 age group in the post-hoc analysis is similar to that in the 9 to 16 year old group, with high estimates of efficacy. This provides supportive evidence suggesting the efficacy of Dengvaxia in the 6 to 8 year old age group.

7.1.8 Persistence of Efficacy

Table 18 from the NS1 COS summarizes the estimated VE against symptomatic VCD due to any serotype during the SEP, which includes follow-up through 6 years after the first dose of Dengvaxia. In subjects aged 6 to 8 years and classified as dengue seropositive, VE against symptomatic VCD cases during the SEP for 3 out of the 4 methods had 95%CIs that did not cross 0. The 4 VE point estimates ranged from 44.4 to 64.7% in 6 to 8 year old seropositive subjects, which is similar to estimates in seropositive subjects aged 9 to 16 years that ranged from 47.9 to 63. In contrast, for subjects aged 2 to 5 years, all 95%CIs were broad and crossed zero, with two having point estimates that were not protective.

Table 18: VE against VCD due to any serotype during the SEP in subjects aged 6 to 8 years, 9 to 16 years, 2 to 5 years, and 6 to 16 years classified as seropositive - NS1 Supplemental Analyses

Group of age	Method	Dengvaxia n (N)	Placebo n (N)	Vaccine Efficacy (95% CI)	
6-8 years CYD14	MI $PRNT_{50}$ M0 *	35.4 (95.9)	32 (47.5)	44.4	(-8.5, 71.5)
	MI $PRNT_{90}$ M0 †	18.9 (79.8)	28.5 (42.4)	64.7	(21.6, 84.1)
	NS1 (Thr 9) M13‡	30 (92)	32 (42)	55.8	(19.8, 75.7)
	NS1 (Thr 50) M13 §	22 (75)	24 (33)	58.2	(17.2, 78.9)
9 to 16 years CYD14+ CYD15	MI $PRNT_{50}$ M0 *	64.4 (1161)	58.4 (562.2)	47.9	(19.4, 66.3)
	MI $PRNT_{90}$ M0 †	40 (1090.4)	53.5 (544.8)	63.0	(38.1, 77.9)
	NS1 (Thr 9) M13‡	60 (1172)	58 (549)	52.4	(30.8, 67.3)
	NS1 (Thr 50) M13 §	41 (1050)	36 (481)	49.2	(19.4, 68.0)
2 to 5 years CYD14	MI $PRNT_{50}$ M0 *	40.1 (113.3)	18.4 (54.2)	-3.8	(-101.1, 46.4)
	MI $PRNT_{90}$ M0 †	14.2 (72.8)	12.1 (40.5)	36.9	(-82.2, 78.2)
	NS1 (Thr 9) M13‡	38 (115)	17 (44)	15.7	(-61.5, 56.0)
	NS1 (Thr 50) M13 §	19 (69)	7 (33)	-25.7	(-222.2, 51.0)
6 to 16 years CYD14+CYD15	MI $PRNT_{50}$ M0 *	99.8 (1256.9)	90.4 (609.7)	46.9	(22.8, 63.5)
	MI $PRNT_{90}$ M0 †	58.9 (1170.2)	82 (587.2)	64.1	(43.2, 77.3)
	NS1 (Thr 9) M13‡	90 (1264)	90 (591)	53.8	(37.1, 66.0)
	NS1 (Thr 50) M13 §	63 (1125)	60 (514)	52.8	(31.8, 67.4)



n: number of subjects fulfilling the item listed; N: total number of subjects selected in sub-cohort

For MI PRNT50 M0 and MI PRNT90 M0, n and N are average numbers from 10 iterations of multiple imputations

For NS1 (Thr9) M13 and NS1 (Thr50) M13 classification, subjects with symptomatic VCD cases before M13 were excluded from the analyses Study group classified as randomized (Subjects classified according to the injection assigned at randomization)

* Source: modified from 5.3.5.4 NS1 Close-out Report, Table 9.6.9, Table 9.6.12, Table 9.6.13, and Table 9.6.14

† Source: modified from 5.3.5.4 NS1 Close-out Report, Appendix 15, Table 2.10, and 5.3.5.4 NS1 additional outputs, Table 1.6

‡ Source: modified from 5.3.5.4 NS1 Close-out Report, Table 9.6.37, Table 9.6.40, Table 9.6.41, and Table 9.6.42

§ Source: modified from 5.3.5.4 NS1 Close-out Report, Table 9.6.49, Table 9.6.52, Table 9.6.53, and Table 9.6.54

from pg 31 of CO

Reviewer Comment:
Results presented in table 18 convey VE was durable through the SEP. This is not the primary VE analysis or objective, but it is useful to evaluate the persistence of efficacy. VE against all serotypes ranged between 44.4% and 64.7%, and all except one method, MI PRNT50 M0, had CI that did not cross 0. This illustrates that Dengvaxia has efficacy that persists amongst 6 to 8 year old seropositive subjects. Analyses in the 9 to 16 and the pooled 6 to 16 year old age groups demonstrate similar results, but with smaller CIs, and provides supportive evidence of efficacy for 6 to 8 year old individuals, and for the whole 6 to 16 year old range, if the age lowering expansion is approved.

7.1.11 Efficacy Conclusions

The NS1 COS estimated vaccine efficacy against Virologically Confirmed Dengue post dose 3 and in the active phase (from M13 to M25). The vaccine efficacy amongst those designated seropositive in the 6 to 8 year old group ranged from 55.8 to 67.3 for the inferral and imputation methods. In the original clinical trials considered for initial licensure of Dengvaxia, the success criterion for efficacy was a LBCI greater than 25%. In the NS1 COS, the analysis of VE using the imputation methods for determining serostatus yielded a LBCI for VE greater than 25%, while the LBCI for the NS1 inferral approaches were 1.8 and 6.2. These point estimates and the CIs, however, are acceptable and show efficacy as this post-hoc analysis did not prespecify a LBCI >25% and was not powered to exceed this threshold.

Immunogenicity analyses are also supportive of vaccine efficacy, as the increase in GMT post dose 3 in 6 to 8 year old individuals are similar to those observed in 9 to 17 year old seropositive subjects. Additionally, GMTs increased for each of the 4 serotypes after 3 injections of the CYD dengue vaccine among baseline seropositive subjects in both the 6 to 8 year old and 9 to 17 year old age groups.

Analyses of VE against each serotype are also similar to those from the original approval, with better efficacy against serotypes 3 and 4, and lower efficacy against serotype 2. As in the original approval, this analysis and the studies, were not powered to evaluate serotype-specific VE, and the broad CIs can be attributed to the small number of cases identified.

The NS1 COS found Dengvaxia to be efficacious in individuals 6 to 8 years old designated as baseline seropositive. Vaccine efficacy and immunogenicity data in seropositive 6 to 8 years old individuals are similar to the findings in 9 to 16 year old seropositive individuals, which further supports efficacy in the 6 to 8 year old population.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

Reviewer Comment: *Due to the safety signal identified in the original clinical-endpoint efficacy studies of an increased risk of hospitalized and severe dengue in individuals with no prior exposure to dengue who were vaccinated with Dengvaxia, the approved indication requires determining the dengue serostatus of individuals prior to vaccination (i.e., patients need to be dengue seropositive prior to vaccination with Dengvaxia).*

To support an extension of the age indication down to children 6 to 8 years of age, the analyses of safety were updated with the NS1 Close-out Study (COS), which is a pooled, post-hoc, case-cohort analysis of data from clinical trials evaluating the safety and efficacy of CYD dengue vaccine. Please see section 7.1.1 for a more complete description of the NS1 COS study methods.

The NS1 COS safety analysis focuses on estimating the risk of hospitalized and severe dengue vaccination in study participants designated as seropositive at baseline, prior to vaccination. NS1 study utilized multiple methods to determine serostatus at baseline:

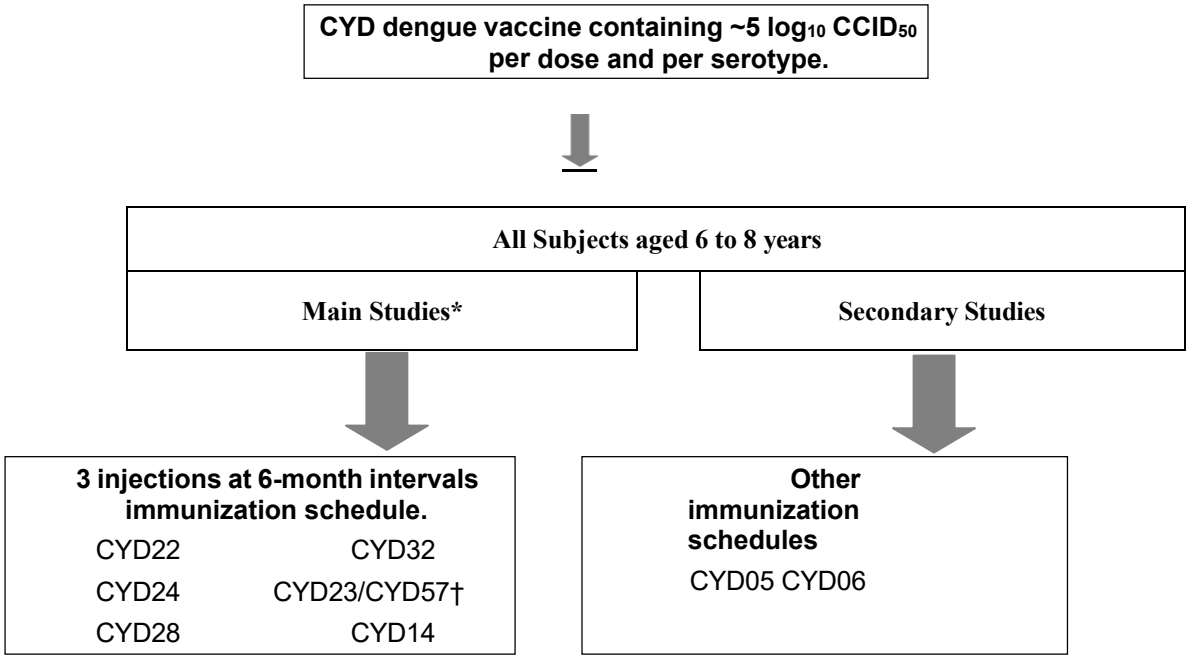
- *Measured or imputed plaque reduction neutralization test (PRNT50) at baseline (M0).*
- *Measured or imputed PRNT90 at M0.*
- *Dengue anti-NS1 IgG ELISA assay readout at M13 (seronegativity defined as an anti-NS1 titer < 9 EU/mL and seropositivity as an anti-NS1 titer ≥ 9 EU/mL).*
- *Strict seropositive classification (strict seropositivity defined anti-NS1 titer ≥ 50 EU/mL at M13).*

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Data from 17 studies using the final formulation and a 3-dose vaccination schedule at Day 0, Month 6 and Month 12 in subjects ≥ 6 years, are referred to in the text as the "Main Studies" and were part of the integrated/pooled analyses.

Figure 1: Main and Secondary Studies Considered for the pooled/integrated analysis of safety in subjects aged 6 to 8 years



* Studies using the final formulation and a 3-dose vaccination schedule D0/M6/M12

† The long-term safety follow-up of subjects from CYD23 was carried out in CYD57 from pg 22 SCS

As seen in figure 1.2 above, studies CYD22, CYD32, CYD24, CYD23/57, CYD28, and CYD14 are the studies that provide the data for the safety analysis in the 6 to 8 year old population.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

Table 19: Summary of subject demographics in subjects aged 6 to 8 years at first injection of the CYD dengue vaccine - SafAS Main Studies CYD Dengue Group

Region	N	Male n (%)	Female n (%)	Mean age (yrs)	M	Asian n (%)	Black n (%)	Caucasian n (%)	Hispanic n (%)	American Indian or Alaska native n (%)	Native Hawaiian or other Pacific Islander n (%)	Other n (%)
All Endemic AP*	3179	1530 (48.1)	1649 (51.9)	7.0	1934	1934 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Endemic LatAm*	54	28 (51.9)	26 (48.1)	6.8	-	-	-	-	-	-	-	-
All Endemic*	3233	1558 (48.2)	1675 (51.8)	7.0	1934	1934 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
All Endemic, baseline seropositive	294	138 (46.9)	156 (53.1)	7.0	191	191 (100.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

N: total number of subjects listed in the first three columns
M: number of subjects who provided ethnicity data
Percentages are based on the number of subjects with available data for the relevant category
Age is calculated at first vaccination regardless of what the subject received
The CYD dengue vaccine Group in Main Studies consists of subjects assigned to a 3-dose CYD dengue vaccine schedule [D0/M6/M12] and who received at least one dose of CYD dengue vaccine.
* Seropositive and seronegative subjects plus subjects with undetermined baseline dengue status or not assessed for baseline dengue status
Source: modified from 5.3.5.3 Integrated Safety Analysis Report, Table 3.11.0.9
from pg 61 SCS

In children aged 6 to 8 years, the distribution between males and females was similar in the data from combined regions for the 3-dose schedule. The mean age of subjects at enrollment for the combined regions was 7.0 years. Among the subjects who provided data on ethnicity in the Asian Pacific region, all subjects were Asian, while in the Latin American region, no ethnic origin data was collected. In the combined regions, 529 subjects had baseline dengue serostatus available, and more than half of subjects were baseline seropositive (n= 294 or 55.6%).

8.2.3 Categorization of Adverse Events

All AEs (including SAEs) in all studies were recoded for the pooled/integrated analysis using the same MedDRA version (22.1).

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

All studies had a similar design, i.e., randomized, controlled studies conducted in healthy subjects. Although the procedures for the collection of safety data have changed in the course of the clinical development program, the time points and main endpoints remained similar enough to allow for an integrated and/or pooled analysis with a majority of the studies included in this submission. The rationale for performing a pooled/integrated analysis was that, with a larger sample size, safety trends could be more precisely analyzed, and safety signals may be detected which might not have been detected at an individual study level.

8.4 Safety Results

8.4.1 Deaths

No death was reported in the CYD dengue vaccine Group within 6 months after any injection in the Main Studies. In the Placebo / Control Group, 5 (0.3%) deaths occurred in the Main Studies within 6 months after any injection (acute lymphoblastic leukemia, drowning, head injury, T-cell lymphoma, and road traffic accident). None were assessed as related to the injection by the Investigator or the Sponsor.

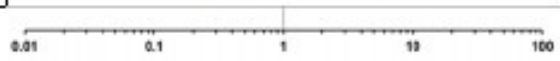
Reviewer Comment:
No safety concern for deaths was evident after CYD vaccination, as no deaths occurred within 6 months of vaccination.

8.4.2 Nonfatal Serious Adverse Events

Table 20 presents the HR estimates against HVCD cases in seropositive subjects aged 6 to 8 years for the 4 approaches, which were consistent and showed a decreased risk of HVCDs in this age group over a 6-year period. HR estimates ranged from 0.210 to 0.404, with the 95% CIs not crossing 1. In comparison, HR estimates in older seropositive children aged 9 to 16 years were slightly lower (from 0.129 to 0.213), while in dengue seropositive subjects aged 2 to 5 years, HR estimates were higher, 0.422 to 0.789, with most approaches crossing 1.

Table 20: Estimated risk of HVCD due to any serotypes during the Entire Study Period - subjects classified as seropositive, and who received at least 1 dose - Pooled Studies - SafAS Efficacy Studies Integrated/Pooled – NS1 Supplemental Analyses (from pg 42 of clinical overview)

Group of age	Method	CYD Dengue Vaccine Group n (N)	Placebo Group n (N)	Risk of HVCD (95% CI)	
6 to 8 years CYD14+ CYD23/57	MI $PRNT_{50}$ M0 *	46 (164.2)	60.6 (84.5)	0.381	(0.208, 0.696)
	MI $PRNT_{90}$ M0 †	19.9 (127.4)	51.1 (70.4)	0.210	(0.112, 0.394)
	NS1 (Thr 9) M13‡	36 (155)	44 (75)	0.404	(0.243, 0.670)
	NS1 (Thr 50) M13 §	23 (123)	30 (56)	0.356	(0.193, 0.657)
9 to 16 years CYD14+ CYD23/57+ CYD15	MI $PRNT_{50}$ M0 *	56.2 (1495.9)	137.1 (729)	0.197	(0.127, 0.306)
	MI $PRNT_{90}$ M0 †	33.4 (1396.8)	128.5 (702.9)	0.129	(0.078, 0.215)
	NS1 (Thr 9) M13‡	51 (1460)	113 (687)	0.213	(0.151, 0.300)
	NS1 (Thr 50) M13 §	31 (1302)	70 (587)	0.201	(0.131, 0.311)
2 to 5 years CYD14+ CYD23/57	MI $PRNT_{50}$ M0 *	40.7 (146.5)	28.1 (70.6)	0.692	0.362, 1.326)
	MI $PRNT_{90}$ M0 †	17.4 (93.9)	22.8 (52.7)	0.422	(0.180, 0.987)
	NS1 (Thr 9) M13‡	40 (149)	23 (60)	0.712	(0.396, 1.279)
	NS1 (Thr 50) M13 §	21 (91)	13 (45)	0.789	(0.368, 1.695)
6 to 16 years CYD14+ CYD23/57+ CYD15	MI $PRNT_{50}$ M0 *	102.2 (1660.1)	197.7 (813.5)	0.251	(0.173, 0.362)
	MI $PRNT_{90}$ M0 †	53.3 (1524.2)	179.6 (773.3)	0.149	(0.099, 0.225)
	NS1 (Thr 9) M13‡	87 (1615)	157 (762)	0.263	(0.200, 0.346)
	NS1 (Thr 50) M13 §	54 (1425)	100 (643)	0.246	(0.175, 0.347)



For all MI approaches, n represents the number of subjects fulfilling the item listed and N represents the total number of subjects selected in sub-cohort; n and N are average numbers from 10 iterations of multiple imputations

For both NS1 M13 approaches, n represents the number of subjects fulfilling the item listed and N represents the total number of subjects selected in sub-cohort. Subjects with VCD cases before M13 were excluded from the analyses

Study group classified as treated (Subjects classified as CYD Dengue Vaccine Group if received at least 1 injection of CYD dengue vaccine)

* Source: modified from 5.3.5.4 NS1 Close-out Report, Table 9.2.126, Table 9.2.125, Table 9.124, and Table 9.2.121

† Source: modified from 5.3.5.4 NS1 Close-out Report, Appendix 15, Table 2.3, and 5.3.5.4 NS1 additional outputs, Table 1.8

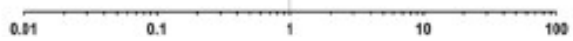
‡ Source: modified from 5.3.5.4 NS1 Close-out Report, Table 9.2.18, Table 9.2.17, Table 9.2.16, and Table 9.2.13

§ Source: modified from 5.3.5.4 NS1 Close-out Report, Table 9.2.30, Table 9.2.29, Table 9.2.28, and Table 9.2.25

Table 21 presents the HR estimates for SVCD in the NS1 Supplemental Analyses. An overall decreased risk of SVCD was observed in seropositive subjects aged 6 to 8 years. The HR estimates were conclusive for 3 out of the 4 approaches, while all 4 had point estimates below 1 (ranging from 0.210 to 0.404). In comparison, HR estimates in older seropositive children aged 9 to 16 years were all conclusive and slightly lower (ranging from 0.96 to 0.168). In contrast, inconclusive results were observed in subjects aged 2 to 5 years with higher SVCD HR point estimates that ranged between 0.523 and 2.201. In the larger population of seropositive subjects aged 6 to 16 years, the decreased risk of SVCD due to any serotype over the entire 6 year follow-up period was confirmed with conclusive estimates for all approaches, as point estimates were between 0.128 and 0.231, and all CIs did not cross 1.

Table 21: Estimated risk of SVCD due to any serotypes during the Entire Study Period - subjects aged 6 to 8 years, 9 to 16 years, 2 to 5 years, and 6 to 16 years, classified as seropositive, and who received at least 1 dose - Pooled Studies - SafAS Efficacy Studies Integrated/Pooled – NS1 Supplemental Analyses

Group of age	Method	CYD Dengue Vaccine Group n (N)	Placebo Group n (N)	Risk of SVCD (95% CI)	
6 to 8 years CYD14+CYD23 /57	MI $PRNT_{50}$ M0 *	8.8 (164.2)	13.2 (84.5)	0.335	(0.106, 1.053)
	MI $PRNT_{90}$ M0 †	5.3 (127.4)	12.8 (70.4)	0.223	(0.068, 0.731)
	NS1 (Thr 9) M13‡	9 (155)	11 (75)	0.400	(0.162, 0.990)
	NS1 (Thr 50) M13 §	4 (123)	8 (56)	0.231	(0.068, 0.783)
9 to 16 years CYD14+CYD23 /57+ CYD15	MI $PRNT_{50}$ M0 *	11.4 (1495.9)	34.2 (729)	0.156	(0.063, 0.391)
	MI $PRNT_{90}$ M0 †	6.3 (1396.8)	32.6 (702.9)	0.096	(0.035, 0.264)
	NS1 (Thr 9) M13‡	10 (1460)	28 (687)	0.168	(0.082, 0.348)
	NS1 (Thr 50) M13 §	5 (1302)	17 (587)	0.134	(0.049, 0.364)
2 to 5 years CYD14+CYD23 /57	MI $PRNT_{50}$ M0 *	13.3 (146.5)	7 (70.6)	0.900	(0.283, 2.858)
	MI $PRNT_{90}$ M0 †	5.6 (93.9)	5.9 (52.7)	0.523	(0.126, 2.180)
	NS1 (Thr 9) M13‡	13 (149)	6 (60)	0.874	(0.320, 2.383)
	NS1 (Thr 50) M13 §	9 (91)	2 (45)	2.201	(0.464, 10.442)
6 to 16 years CYD14+CYD23 /57+ CYD15	MI $PRNT_{50}$ M0 *	20.2 (1660.1)	47.4 (813.5)	0.203	(0.096, 0.429)
	MI $PRNT_{90}$ M0 †	11.6 (1524.2)	45.4 (773.3)	0.128	(0.058, 0.282)
	NS1 (Thr 9) M13‡	19 (1615)	39 (762)	0.231	(0.133, 0.401)
	NS1 (Thr 50) M13 §	9 (1425)	25 (643)	0.164	(0.076, 0.353)



For all MI approaches, n represents the number of subjects fulfilling the item listed and N represents the total number of subjects selected in sub-cohort; n and N are average numbers from 10 iterations of multiple imputations

For both NS1 M13 approaches, n represents the number of subjects fulfilling the item listed and N represents the total number of subjects selected in sub-cohort. Subjects with VCD cases before M13 were excluded from the analyses

Study group classified as treated (Subjects classified as CYD Dengue Vaccine Group if received at least 1 injection of CYD dengue vaccine)

* Source: modified from 5.3.5.4 NS1 Close-out Report, Tables 9.3.79, 9.3.82, 9.3.83, and 9.3.84

† Source: modified from 5.3.5.4 NS1 Close-out Report, Appendix 15, Table 2.6, and NS1 additional outputs, Table 1.2

‡ Source: modified from 5.3.5.4 NS1 Close-out Report, Tables 9.3.13, 9.3.16, 9.3.17, and 9.3.18

§ Source: modified from 5.3.5.4 NS1 Close-out Report, Tables 9.3.25, 9.3.28, 9.3.29, and 9.3.30

from pg 47 of clinical overview

Reviewer Comment:
These analyses demonstrate no increased risk of HVCD or SVCD in subjects 6 to 8 years old. For all the HVCD and SVCD analyses in 6 to 8 year old individuals, the point estimates were below 1, and Dengvaxia was protective. For the HVCD estimates, all 4 CI did not cross 1 while for SVCD three out of four did not cross one. In the NS1 Thr 9 SVCD analysis, whose 95% CI did cross one, it just did so with a higher bound of 1.053.

The clustering/consistency of point estimates for the risk of HVCD/SVCD (ranging from 0.231 to 0.400 for SVCD, and 0.210 to 0.404 for HVCD) for the various approaches to determine seropositivity in the NS1 COS analyses supports the vaccine being protective in the seropositive 6 to 8 year old age group. So the increased risk of HVCD or SVCD that was observed in the seronegative population as part of the original approval, is not evident in this population. These findings are in line with the analyses which supported the original approval in seropositive individuals 9 to 16 years old, as in this population, the risk of SVCD and HVCD was 0.18 and 0.206, respectively.

In addition, similar findings in the immunogenicity subset (IS), supports the protective nature of Dengvaxia against HVCD and SVCD in this age group. In seropositive subjects aged 6 to 8 years in the immunogenicity subset, the relative risk (RR) estimate was 0.378 for HVCD which is consistent with the NS1 COS analysis point estimates from the different approaches in 6 to 8 year old individuals, ranging from 0.210 to 0.404. Similarly, the HR of SVCD NS1 COS estimates, 0.223 to 0.400, were consistent with the RR estimate in the IS of 0.360. As the IS analyses were not powered for these analyses, however, the CIs crossed 1.

Lastly, the findings in the seropositive population contrasts with analyses in the seronegative population, as point estimates of the risk of HVCD varied between 1.531 and 1.949, and point estimates of the risk of SVCD were between 2.483 and 2.752.

Taken together, in 6 to 8 year old individuals designated seropositive at baseline, the consistency of point estimates for risk of HVCD and SVCD; the similarity of findings within the IS analyses; and the contrasting elevated risk observed in seronegative 6 to 8 year old individuals indicates the vaccine is protective in seropositive 6 to 8 year old individuals and that there is no increased risk of HVCD or SVCD in this population.

Of note, and in contrast, the pattern of data in 2 to 5 years was not supportive of the vaccine, and did not demonstrate a decreased risk of SVCD and HVCD in 2 to 5 year old seropositives, as 3 out of 4 analyses of HVCD crossed 1, and for SVCD all four CI crossed one, with one point estimate also being greater than one at 2.201.

Other Serious AEs

The frequency and nature of non-fatal SAEs (excluding clinically severe and hospitalized dengue) in 6 to 8 year old subjects reported within 28 days of vaccination or between 28 days and 6 months after any of the 3 doses were similar between the Dengvaxia, Placebo, and Control groups (table 21). Reported AEs corresponded to common medical conditions such as infections and gastrointestinal complaints. In the Dengvaxia group, 1.3% of subjects 6 through 8 years reported at least one SAE within 28 days after any dose, and 5.6% of subjects 6 through 8 years reported at least one SAE from 28 days to 6 months after any dose. One SAE in the 6 to 8 years old age group was considered related to CYD vaccination, and described a case of acute disseminated

encephalomyelitis on day 7 after the first injection. The event lasted 14 days, led to discontinuation from the study, and the subject fully recovered. No SAEs were assessed as related to the study vaccine by the Investigator between 28 days and 6 months after any dose.

Table 22: Safety overview after any of 3 doses of CYD dengue vaccine or Placebo or Control, regardless of baseline dengue serostatus - Subjects 6 to 8 years - SafAS Main Studies Pooled

	CYD dengue vaccine			Placebo			Control		
Subjects experiencing at least one:	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
SAE <=28 days	41/3233	1.3	(0.91; 1.72)	28/1505	1.9	(1.24; 2.68)	29/1597	1.8	(1.22; 2.60)
SAE >28 days to 6 months post dose	181/323	5.6	(4.83; 6.45)	105/150	7.0	(5.74; 8.38)	110/159	6.9	(5.69; 8.24)
Related SAE <=28 days	1/3233	<0.1	(0.00; 0.17)	2/1505	0.1	(0.02; 0.48)	2/1597	0.1	(0.02; 0.45)
Related SAE >28 days to 6 months post dose	0/3233	0.0	(0.00; 0.11)	0/1505	0.0	(0.00; 0.24)	0/1597	0.0	(0.00; 0.23)

n: number of subjects experiencing the endpoint
M: number of subjects with available data for the relevant endpoint
CYD dengue vaccine 5 ± 1 log10 CCID50 of serotypes 1, 2, 3 and 4

Reviewer Comment:
SAE data among the 6 to 8 year old group occurred at a similar rate as Placebo and Control groups, and did not demonstrate any clustering suggestive of a new safety concern.

The ADEM case occurred in an 8 year old male who was afebrile at the time of vaccination. Seven days later the subject had headache and lethargy, but no fever. Two days later while at school, he had a seizure, ultimately experiencing a total of 4 episodes. The patient remained afebrile and was hospitalized. The neurological exam was notable for a Glasgow Coma Scale of 11/15, neck stiffness, and left upper limb hemiparesis with strength of 2/5. Tone and reflexes were generally normal. Babinski normal bilaterally. Temperature was 36.8 degrees Celsius at admission, with the highest recording during hospitalization being 37.8. The patient was started on oral maintenance dose of oral phenytoin with plan to wean off anticonvulsant after 3 months if no further seizures occurred.

There is no family history of neurologic disorders. There were no preceding infections, except for chickenpox two months prior to vaccination. The last known vaccination for the subject prior to inclusion in the study was at the beginning of 2010, when he was given DTaP, BCG, IPV.

The MRI scan of his brain showed ill-defined increased signal intensities in both caudate and anterior lentiform nuclei, as well as anterior limb of right internal capsule on T2W and FLAIR, which suggested ADEM. Blood cultures, serologies, and PCR identified no infection. The pediatric neurologist diagnosed ADEM. Patient was discharged after a 2 week hospitalization with no neurological deficits.

One ADEM case also occurred among the placebo group in CYD15, in a 13 year old, 5 months after the third placebo dose. This patient also was afebrile, and an MRI diagnosed ADEM.

There is no clustering in the clinical trial data to suggest a new safety concern, as one case of ADEM occurred in the vaccination group and one in the placebo group. In addition, no cases of ADEM have been reported in postmarketing data after Dengvaxia administration. This reviewer suggests adding information about the post-vaccination case to the prescribing information, and routine postmarketing pharmacovigilance activities, as the ADEM case does not suggest a new safety signal.

8.4.3 Study Dropouts/Discontinuations

In the CYD dengue vaccine Group, SAEs led to discontinuation in 4 subjects (rheumatic heart disease, acute disseminated encephalomyelitis, ischemic stroke, and nephrotic syndrome). Four non-serious AEs led to discontinuation in 4 subjects in the CYD group. The AE forms reported 2 cases of urticaria, 1 case of itching rash, and 1 report of illness after vaccination without further explanation. In the Placebo Group, SAEs led to study discontinuation in 10 subjects, and non-serious AEs did in 2 subjects. No trend or clustering of AEs suggesting a safety concern were identified.

8.4.4 Common Adverse Events

Please see section 8.4.6, Systemic Adverse Events, and section 8.4 7, Local Reactogenicity.

8.4.6 Systemic Adverse Events

Solicited systemic reactions within 14 days after any CYD dengue vaccine, placebo, or control injection are presented in children aged 6 to 8 years in the Main Studies, regardless of baseline serostatus, by maximum intensity in the table 23.

Table 23: Solicited systemic reactions after any of 3 doses of CYD dengue vaccine or Placebo or Control, regardless of baseline dengue serostatus, by maximum intensity during the solicited period - Subjects 6 to 8 years - RS Main Studies Pooled

		CYD dengue vaccine			Placebo			Control		
Subjects experiencing at least one:	**Maximum intensity**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Fever		150/766	19.6	(16.8; 22.6)	52/278	18.7	(14.3; 23.8)	58/370	15.7	(12.1; 19.8)
	Grade 1	83/766	10.8	(8.7; 13.3)	20/278	7.2	(4.4; 10.9)	22/370	5.9	(3.8; 8.9)
	Grade 2	43/766	5.6	(4.1; 7.5)	20/278	7.2	(4.4; 10.9)	23/370	6.2	(4.0; 9.2)
	Grade 3	24/766	3.1	(2.0; 4.6)	12/278	4.3	(2.3; 7.4)	13/370	3.5	(1.9; 5.9)
Headache		394/765	51.5	(47.9; 55.1)	136/278	48.9	(42.9; 55.0)	177/370	47.8	(42.6; 53.1)
	Grade 1	304/765	39.7	(36.3; 43.3)	103/278	37.1	(31.4; 43.0)	136/370	36.8	(31.8; 41.9)
	Grade 2	73/765	9.5	(7.6; 11.8)	23/278	8.3	(5.3; 12.2)	30/370	8.1	(5.5; 11.4)
	Grade 3	17/765	2.2	(1.3; 3.5)	10/278	3.6	(1.7; 6.5)	11/370	3.0	(1.5; 5.3)
Malaise		338/765	44.2	(40.6; 47.8)	109/278	39.2	(33.4; 45.2)	143/370	38.6	(33.7; 43.8)
	Grade 1	253/765	33.1	(29.7; 36.5)	82/278	29.5	(24.2; 35.2)	112/370	30.3	(25.6; 35.2)
	Grade 2	73/765	9.5	(7.6; 11.8)	18/278	6.5	(3.9; 10.0)	22/370	5.9	(3.8; 8.9)
	Grade 3	12/765	1.6	(0.8; 2.7)	9/278	3.2	(1.5; 6.1)	9/370	2.4	(1.1; 4.6)
Myalgia		307/765	40.1	(36.6; 43.7)	96/278	34.5	(29.0; 40.4)	128/370	34.6	(29.8; 39.7)
	Grade 1	252/765	32.9	(29.6; 36.4)	81/278	29.1	(23.9; 34.9)	108/370	29.2	(24.6; 34.1)
	Grade 2	47/765	6.1	(4.5; 8.1)	8/278	2.9	(1.3; 5.6)	13/370	3.5	(1.9; 5.9)
	Grade 3	8/765	1.0	(0.5; 2.1)	7/278	2.5	(1.0; 5.1)	7/370	1.9	(0.8; 3.9)
Asthenia		251/765	32.8	(29.5; 36.3)	90/278	32.4	(26.9; 38.2)	108/370	29.2	(24.6; 34.1)
	Grade 1	189/765	24.7	(21.7; 27.9)	62/278	22.3	(17.5; 27.7)	79/370	21.4	(17.3; 25.9)
	Grade 2	53/765	6.9	(5.2; 9.0)	17/278	6.1	(3.6; 9.6)	18/370	4.9	(2.9; 7.6)
	Grade 3	9/765	1.2	(0.5; 2.2)	11/278	4.0	(2.0; 7.0)	11/370	3.0	(1.5; 5.3)

Table summarizes worst case for a subject which is the maximum intensity observed from each dose n: number of subjects experiencing the endpoint
M: number of subjects with available data for the relevant endpoint
CYD dengue vaccine 5 ± 1 log10 CCID50 of serotypes 1, 2, 3 and 4
Main studies applied a D0/M6/M12 vaccine schedule
Contributing studies: CYD14 CYD22 CYD23 CYD24 CYD28 CYD32
Source: Reproduced from 5.3.5.3 Integrated Safety Analysis Report, Table 3.11.1.22.
from pg 101 of SCS

The most frequent solicited systemic reaction within 14 days after any CYD dengue vaccine injection was headache (51.5%), while malaise (44.2%), myalgia (40.1%), asthenia (32.8%) and fever (19.6%) were less frequently reported.

Most solicited systemic reactions were Grade 1, occurred within 3 days after injection (except for fever, which appeared throughout the solicited period) and had between 1 and 3 days of duration. Grade 3 fever occurred throughout the solicited period D0 to D14 and resolved after 1 to 3 days.

In the Placebo and Control Groups, the incidence of solicited systemic reactions were similar compared to the CYD dengue vaccine Group for fever (~19 %), headache (~50%), and asthenia (~30%), and slightly lower for malaise (~40%) and myalgia (~35%). The maximum intensity, time to onset, and number of days of occurrence were similar in the CYD dengue vaccine, Placebo, and Control Groups.

In a subanalysis of baseline seropositive subjects, the solicited systemic reactions were reported with similar frequencies in the CYD dengue vaccine, Placebo, and Control Groups for headache (42.5%, 41.8%, 43.4%, respectively), malaise (34.9%, 30.9%, and 32.9%, respectively), and asthenia (24.3%, 22.7%, and 25.0%, respectively). For fever and myalgia, rates in the Placebo and Control Groups were slightly lower compared to the CYD group (~12% vs. 19% for fever and ~25% vs. 33%).

Reviewer Comment:
Solicited systemic reactions in the Dengvaxia group occurred at comparable rates and intensities as Placebo and Control groups in analyses of the 6 to 8 year old individuals regardless of baseline serostatus. In subanalyses of seropositive 6 to 8 year old individuals administered Dengvaxia, similar rates were also observed compared to the Placebo and Control groups. The safety data demonstrated that there are no new safety concerns identified for systemic reactions in the 6 to 8 year old individuals administered Dengvaxia.

8.4.7 Local Reactogenicity

Solicited injection site reactions within 7 days after any CYD dengue vaccine, placebo, or control injection, regardless of baseline serostatus, are presented by maximum intensity in Table 24.

The most frequent solicited injection site reaction within 7 days after any CYD dengue vaccine injection was injection site pain (51.4% of subjects), while erythema (21.7%) and swelling (16.2%) were less frequently reported. Most solicited injection site reactions were Grade 1, occurred within 3 days after injection and had between 1 and 3 days of duration. A total of 3 (0.4%) subjects experienced Grade 3 injection site reactions due to pain.

In the Placebo and Control Groups, injection site pain was also the most frequent solicited injection site reaction and was reported at a similar rate of 48.9% and 51.4% of subjects, respectively. Erythema (24.1% and 22.7%) and swelling (16.5% in both groups) were also reported at similar frequencies as the CYD dengue vaccine Group. For all solicited injection site reactions, the maximum intensity, time to onset, and number of days of occurrence were similar in the CYD dengue vaccine, Placebo, and Control Groups.

Table 24: Solicited injection site reactions after any of 3 doses of CYD dengue vaccine or Placebo or Control, regardless of baseline dengue serostatus, by maximum intensity during the solicited period - Subjects 6 to 8 years - RS Main Studies Pooled

		CYD dengue vaccine			Placebo			Control		
Subjects experiencing at least one:	**Maximum intensity**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**	**n/M**	**%**	**(95% CI)**
Pain		394/766	51.4	(47.8; 55.0)	136/278	48.9	(42.9; 55.0)	190/370	51.4	(46.1; 56.6)
	Grade 1	369/766	48.2	(44.6; 51.8)	128/278	46.0	(40.1; 52.1)	176/370	47.6	(42.4; 52.8)
	Grade 2	22/766	2.9	(1.8; 4.3)	8/278	2.9	(1.3; 5.6)	12/370	3.2	(1.7; 5.6)
	Grade 3	3/766	0.4	(0.1; 1.1)	0/278	0.0	(0.0; 1.3)	2/370	0.5	(0.1; 1.9)
Erythema		166/766	21.7	(18.8; 24.8)	67/278	24.1	(19.2; 29.6)	84/370	22.7	(18.5; 27.3)
	Grade 1	163/766	21.3	(18.4; 24.4)	63/278	22.7	(17.9; 28.0)	77/370	20.8	(16.8; 25.3)
	Grade 2	3/766	0.4	(0.1; 1.1)	4/278	1.4	(0.4; 3.6)	5/370	1.4	(0.4; 3.1)
	Grade 3	0/766	0.0	(0.0; 0.5)	0/278	0.0	(0.0; 1.3)	2/370	0.5	(0.1; 1.9)
Swelling		124/765	16.2	(13.7; 19.0)	46/278	16.5	(12.4; 21.4)	61/370	16.5	(12.9; 20.7)
	Grade 1	119/765	15.6	(13.1; 18.3)	44/278	15.8	(11.7; 20.7)	57/370	15.4	(11.9; 19.5)
	Grade 2	4/765	0.5	(0.1; 1.3)	1/278	0.4	(0.0; 2.0)	1/370	0.3	(0.0; 1.5)
	Grade 3	1/765	0.1	(0.0; 0.7)	1/278	0.4	(0.0; 2.0)	3/370	0.8	(0.2; 2.4)

Table summarizes worst case for a subject which is the maximum intensity observed from each dose
n: number of subjects experiencing the endpoint
M: number of subjects with available data for the relevant endpoint
CYD dengue vaccine 5 ± 1 log10 CCID50 of serotypes 1, 2, 3 and 4
Main studies applied a D0/M6/M12 vaccine schedule
Contributing studies: CYD14 CYD22 CYD23 CYD24 CYD28 CYD32
Source: modified from 5.3.5.3 Integrated Safety Analysis Report, Table 3.11.1.15.
from pg 99 of SCS

In sub analyses of baseline seropositive subjects, the same pattern was evident, with solicited injection site reactions, as they were reported with similar frequencies in the three groups. For example, pain was reported most frequently: 46.1%, 37.3%, and 42.8% in the CYD dengue vaccine, Placebo, and Control Groups respectively.

Reviewer Comment:
Solicited injection site reactions in the Dengvaxia group occurred at comparable rates and intensities as Placebo and Control groups in analyses of the 6 to 8 year old individuals regardless of baseline serostatus. In subanalyses of seropositive 6 to 8 year old individuals administered Dengvaxia, similar rates were also observed compared to the Placebo and Control groups. The safety data demonstrated that there are no new safety concerns identified for injection site reactions in the 6 to 8 year old individuals administered Dengvaxia.

8.4.8 Adverse Events of Special Interest

The following AESIs were monitored: allergic reactions within 7 days after vaccine injection; viscerotropic or neurotropic events within 30 days after vaccine injection, and serious dengue disease (SDD). SDD was covered in section 8.4.2 in the analyses of risk of SVCD and HVCD.

For allergic reactions, no subjects aged 6 to 8 years in the CYD dengue vaccine Group experienced anaphylaxis or a serious allergic reaction. For non-serious allergic reactions 6 subjects out of 768 (0.8%) experienced reactions, and 2 were considered related to the vaccine (rash and urticaria).

A total of 9 SAEs occurring in subjects aged 6 to 60 years within 30 days from any injection were investigated for suspected neurotropism or viscerotropism. There were 4 suspected cases in the CYD dengue vaccine Group and 5 in the Placebo Group. In all biological specimens from these subjects, genomic amplification was negative for vaccinal virus and/or wild type yellow fever virus strains. So in the CYD vaccine studies generally, and specifically among subjects aged 6 to 8 years at enrollment, no events of viscerotropic or neurotropic disease were observed after administration of the CYD dengue vaccine.

Reviewer Comment:
No risk of severe allergic reactions, viscerotropic disease, or neurotropic disease was identified among 6 to 8 year old individuals after administration of Dengvaxia.

8.5.9 Person-to-Person Transmission, Shedding
Shedding was assessed in the original approval memo. It stated that 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 samples from 2 subjects.

There were no safety concerns noted in the relevant 2 subjects, and no replication-competent dengue vaccine virus was detected in any sample, so there is no identified safety concern due to viral shedding.

8.6 Safety Conclusions

As previously stated, the age lowering submission contains no new clinical studies, instead the sponsor submitted the NS1 Close-out study, a post-hoc study, which utilizes a case-cohort study design, and inferral (NS1) and imputation methods to estimate baseline serostatus in previously conducted clinical trials in which subjects received either CYD dengue vaccine or placebo (CYD14, CYD15, and CYD23/57). Consideration of efficacy and risk by serostatus is necessary for Dengvaxia, as the initial approval was limited to use in seropositive 9 to16 year old individuals due to the observation of an increased risk of severe dengue in vaccinated individuals who were seronegative at baseline.

The NS1 COS safety analyses demonstrated no increased risk of HVCD or SVCD in subjects 6 to 8 years old, as for all the inferral and imputation based analyses of HVCD and SVCD in seropositive 6 to 8 year old individuals, the point estimates were below 1, and Dengvaxia was protective. In addition, for 7 out of 8 of the inferral/imputation based analyses, the 95% CI for the risk of HVCD and SVCD did not cross 1. For one of the

SVCD that did have a CI that crossed 1(the NS1 Thr 9 SVCD analysis) it just slightly crossed 1 with a higher bound of 1.053.

These findings are in line with the analyses which supported the original approval in seropositive individuals 9 to 16 years old, as in this population, there was no increased risk of SVCD and HVCD. Furthermore, in seropositive subjects aged 6 to 8 years in the immunogenicity subset (IS), the RR estimate was 0.378 for HVCD, which is consistent with the NS1 COS analysis point estimates for seropositive 6 to 8 year old individuals, as these ranged from 0.210 to 0.404. Similarly, the risk of SVCD in NS1 COS estimates varied between 0.223 and 0.400, which is consistent with the RR estimate in the IS of 0.360.

These findings contrast with findings in analyses of the seronegative population, which were greater than one and demonstrated an increased risk of HVCD and SVCD. In the 6 to 8 year old seronegative group, point estimates of the risk of HVCD varied between 1.531 and 1.949, and point estimates of the risk of SVCD were between 2.483 and 2.752.

Additionally, the NS1 COS analyses of seropositive 2 to 5 year old individuals were not supportive of the vaccine, and did not demonstrate a decreased risk of SVCD and HVCD, instead, 3 out of 4 analyses of HVCD had CIs that crossed 1, while all four SVCD analyses had CIs that crossed one, with one of the point estimates also being greater than one at 2.201.

Lastly, review of AE data revealed no safety issue with Dengvaxia due to solicited local/systemic reactions, SAEs, AESIs (severe allergic reactions, viscerotropic disease, or neurotropic disease), or deaths.

Taken together, the consistency of point estimates for the lack of increased risk of HVCD and SVCD in seropositive 6 to 8 year old individuals; the similarity of findings with analyses of seropositives in the IS analyses; and the contrasting elevated risk observed in seronegative 6 to 8 year old individuals indicated the vaccine is protective in seropositive 6 to 8 year old individuals, and that there is no increased risk of HVCD or SVCD in this population. Again, these findings are consistent with the findings of efficacy, and the lack of a safety concern in seropositive 9 to 16 year old individuals, which was the basis of the original approval.

The NS1 COS analyses are supportive of the adequate safety of Dengvaxia in 6 to 8 year old dengue seropositive individuals.

9. ADDITIONAL CLINICAL ISSUES

9.1.3 Pediatric Use and PREA Considerations

The May 2019 approval letter granted a waiver of the requirement for an assessment for the age group 0 to 6 months, and deferred the assessment for the age group 6 months to < 9 years. The Sponsor was originally granted a waiver for birth to six months of age because studies are impossible or highly impractical due to the number of pediatric patients who would be both infected with Dengue and have laboratory confirmation of infection in this age group being both small and geographically dispersed. The Sponsor received deferrals for age six months to less than 2 years and from 2 years of age to

less than 9 years of age, and was required to conduct four PREA required studies to complete necessary analyses of safety and effectiveness.

This submission satisfied the deferral for ages 2 to less than 9 years of age, and fulfills the requirement to conduct PREA PMRs in this age group. Due to the COVID pandemic, the required study in 6 months to less than 2 years of age was not started, and in light of findings of lack of safety among seropositives in the 2 to 5 year old age group (an increased risk SVCD and HVCD), the completion of this study was deemed unnecessary by the PeRC, and the PeRC granted a release from the study requirement and a waiver for this age group.

With waivers from 0 to 2 years of age, and the study requirements for ages 2 to less than 9 years of age fulfilled, the sponsor has satisfied the pediatric study requirement for this application.

10. CONCLUSIONS

The age lowering submission contains no new pivotal studies, instead the sponsor submitted the NS1 Close-out study (COS), a post-hoc study, which utilizes a case-cohort study design, and inferral (using the NS1 laboratory test) and imputation methods to estimate baseline serostatus in previously conducted clinical trials. The inferral/imputation approach increased the amount of data available for analyses and helps power the NS1 COS to evaluate safety and efficacy in seropositive 6 to 8 year old individuals, the age group and serostatus being considered for inclusion in the Dengvaxia indication.

The NS1 COS categorized serostatus in the following ways, Inferred:

- Dengue anti-NS1 IgG ELISA assay readout at M13 (seronegativity defined as an anti-NS1 titer < 9 EU/mL and seropositivity as an anti-NS1 titer ≥ 9 EU/mL).
- Strict seropositive classification (strict seropositivity defined anti-NS1 titer ≥ 50 EU/mL at M13).

And imputed (or measured for those subjects with blood samples drawn at baseline):

- Measured or imputed plaque reduction neutralization test (PRNT50) at baseline (M0).
- Measured or imputed PRNT90 at M0.

In the NS1 COS, the vaccine efficacy amongst those designated seropositive in the 6 to 8 year old group ranged from 55.8 to 67.3 for the four different serostatus inferral and imputation methods. In the original clinical trials considered for initial licensure of Dengvaxia, the success criterion for efficacy was a Lower Bound of the Confidence Interval greater than 25%, and in the NS1 COS, the analysis of VE using the imputation methods for determining serostatus yielded a LBCI for VE greater than 25%, while the LBCI for the NS1 inferral approaches were 1.8 and 6.2. These point estimates and the CIs, however, are acceptable and show efficacy as this post-hoc analysis did not prespecify a LBCI >25% and was not powered to exceed this threshold.

The NS1 COS safety analyses demonstrated no increased risk of HVCD or SVCD in subjects 6 to 8 years old, as for all of the inferral and imputation based analyses of HVCD and SVCD in seropositive 6 to 8 year old individuals, the point estimates were below 1, and Dengvaxia was protective. In addition, for 7 out of 8 of the inferral/imputation based analyses, the 95% CI for the risk of HVCD and SVCD did not

cross 1. For one of the SVCD analyses that did have a CI that crossed 1 (the NS1 Thr 9 SVCD analysis) it just slightly crossed 1 with a higher bound of 1.053.

These findings contrast with findings in analyses of the seronegative population. In the 6 to 8 year old seronegative group, point estimates of the risk of HVCD varied between 1.531 and 1.949, and point estimates of the risk of SVCD were between 2.483 and 2.752. These analyses indicate Dengvaxia is not safe in seronegative 6 to 8 year old individuals.

In summary, the NS1 COS analyses in dengue seropositive subjects 6 to 8 years old pre-vaccination demonstrated efficacy against VCD without any increased risk in HVCD or SVCD. Conversely, in the 6 to 8 year old subjects who were dengue seronegative pre-vaccination, an increased risk of HVCD and SVCD was observed. This is similar to findings in the original approval in 9 to 16 year old individuals residing in dengue endemic regions, and who have laboratory confirmation of a previous dengue infection. CBER recommends approval of lowering the age of Dengvaxia to include 6 to 8 year old dengue seropositive individuals, so the indication would cover individuals 6 through 16 years of age, residing in dengue endemic regions, and who have laboratory confirmation of a previous dengue infection.

11. RISK-BENEFIT CONSIDERATIONS AND RECOMMENDATIONS

11.1 Risk-Benefit Considerations

The Risk-Benefit considerations are discussed in Table 25 below:

Table 25. 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, which can result in 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. • 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 is the first dengue vaccine licensed and available in the US. • There will remain an unmet medical need for dengue prevention in individuals 0-6 years of age and >17 years of age because of the age indication of 6 through 16 years for Dengvaxia. • There will remain an unmet medical need for a preventive Dengue Vaccine in individuals who have never had a prior Dengue infection
Clinical Benefit	• The NS1 Close-out study (COS), a post-hoc study, which utilizes a case-cohort study design, and inferral (NS1) and imputation methods to estimate baseline serostatus in previously conducted clinical trials (CYD14, CYD15, and CYD23/CYD57) demonstrated the effectiveness of Dengvaxia in dengue seropositive individuals 6 through 8 years of age. This expands established efficacy and safety from the original approval in dengue seropositive individuals 9 to 16 years of age.	• VE data from the NS1 post-hoc study included in this BLA support the effectiveness of Dengvaxia to prevent dengue disease caused by serotypes 1, 2, 3 and 4 in individuals 6 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 6 to 8 years of age who were dengue seronegative at baseline. • There is a decreased RR for severe/hospitalized dengue post-vaccination in subjects 6 to 8 years of age who were dengue seropositive at baseline.	• The available evidence supports the safety of Dengvaxia in dengue seropositive individuals 6 to 8 years of age (in addition to the original approval for ages 9 to 16 years of age). • 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. • This risk can be mitigated by requiring laboratory confirmation of a prior dengue infection before vaccination, and by limiting the indication to individuals over the age of 6 years, as the prevalence of individuals with at least one prior dengue infection increases with age in endemic areas.	• Limiting use to dengue seropositive individuals in endemic areas adequately mitigates risks associated with vaccination of dengue seronegative individuals. • Limiting use to individuals between the ages of 6 and 16 adequately mitigates risk associated with vaccination in lower age groups, where the prevalence of dengue seropositivity is lower.

11.2 Risk-Benefit Summary and Assessment

The NS1 COS analysis in this sBLA demonstrated the efficacy of Dengvaxia in dengue seropositive individuals 6 to 8 years of age living in endemic areas. Within the same population, the safety profile of Dengvaxia is acceptable and is adequately described in the package insert. The overall risk-benefit is favorable. Continued safety surveillance through routine pharmacovigilance is sufficient.

11.3 Discussion of Regulatory Options

The regulatory options for this application are to approve the application for the indication as requested for 6 to 8 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.

Dengvaxia was previously approved for dengue seropositive individuals 9 to 16 years of age living in endemic areas. The efficacy and safety analyses presented in this submission support the approval of use in dengue seropositive individuals 6 to 8 years of age living in endemic areas, so use in ages 6 to 16 years of age would be approved in the updated indication.

11.4 Recommendations on Regulatory Actions

This clinical reviewer recommends approval of Dengvaxia for use in dengue seropositive individuals 6 to 8 years of age living in endemic areas, so the updated indication would allow use in seropositive individuals ages 6 to 16 years of age.

11.5 Labeling Review and Recommendations

The prescribing information was reviewed during this sBLA review and specific comments on the labeling were provided by CBER to the applicant who made requested revisions.

The following changes were made to the label; under “Indications and Usage” the label now states Dengvaxia is approved for use in individuals 6 through 16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas; vaccine efficacy and safety data from this submission were also added to the label. Please see the final approved PI for the final agreed upon language.

11.6 Recommendations on Postmarketing Actions

No additional post-marketing studies are needed as a result of the clinical review of the safety and immunogenicity data in this sBLA. The submitted PVP, which describes continued routine pharmacovigilance, is adequate.