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Application Type	BLA Supplement
STN	125682/40
CBER Received Date	May 31, 2022
PDUFA Goal Date	June 30, 2023
Division / Office	DVRPA /OVRR
Committee Chair	Joseph Temenak
Clinical Reviewer(s)	Ravi Goud
Project Manager	Brynn Hollingsworth
Priority Review	No
Reviewer Name(s)	Laura Thompson, Ph.D.
Review Completion Date / Stamped Date	
Concurrence	Lei Huang, Ph.D. Concurring Reviewer, VEB, DB, OBPV
Concurrence	Tsai-Lien Lin, Ph.D. Chief, VEB, DB, OBPV
Applicant	Sanofi Pasteur Inc.
Established Name	Dengue Tetravalent Vaccine, Live
(Proposed) Trade Name	Dengvaxia
Pharmacologic Class	Viral Vaccines
Formulation(s), including Adjuvants, etc	Suspension for injection (0.5 mL) supplied as a lyophilized powder to be reconstituted with the supplied diluent.
Dosage Form(s) and Route(s) of Administration	The 3-dose immunization series consists of a 0.5 mL subcutaneous injection administered at 6-month intervals (month 0, 6, and 12).
Dosing Regimen	3 injections of 0.5 mL to be administered at 6-month intervals
Indication(s) and Intended Population(s)	for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3, and 4 in individuals 6 through 16 years of age living in endemic areas, and is recommended for individuals with prior dengue virus infection

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GLOSSARY

AR Adverse Reaction
CV Cross validated
CYD Chimera yellow fever dengue
DPM Dirichlet Process Mixture
ELISA Enzyme-linked immunoassay
FASE Full Analysis set for Efficacy
FASI Full Analysis set for Efficacy (Immunogenicity Subset)
GMT Geometric Mean Titer
GMTR Geometric Mean Titer Ratio
HR Hazard Ratio
HVCD Hospitalized Virologically-confirmed Dengue
MI Multiple Imputation
PD3 Post-dose 3
PRNT Plaque reduction neutralization test
RR Relative Risk
SAE Serious adverse event
SEP Surveillance Expansion Period
SVCD Severe Virologically-confirmed Dengue
VCD Virologically-confirmed Dengue
VE Vaccine Efficacy
WT Wild-type

1. EXECUTIVE SUMMARY

This Supplement to BLA 125682 requests to extend the indication of CYD Dengue Vaccine to seropositive children 6 – 8 years of age, from 9 – 16 years of age. To support the extension of the age indication down to children 6 to 8 years of age, the integrated analyses of safety, immunogenicity, and efficacy were updated with new available data and analysis results including 1) final results (long-term follow-up data) of the 2 pivotal efficacy studies CYD14 and CYD15 and 2) final results of the NS1 Supplemental Analyses used to support the extension of the age indication down to children 6 to 8 years of age. Additional studies (namely, CYD65, CYD67, and CYD71), which included subjects aged above 9 years, were used for the comparison of results from CYD14 and CYD23/57 in subjects aged 6 to 8 years with those in subjects aged 9 years and above. The primary endpoints in support of the extended indication were VE against symptomatic virologically confirmed dengue (VCD), relative risk (RR) for hospitalized VCD (HVCD) and RR for severe VCD (SVCD). However, baseline serostatus measured via PRNT50 was only available in a subset of subjects (i.e., the Immunogenicity Subset) from the main efficacy studies. Baseline serostatus was missing in about 65% of subjects aged 6 to 8 years. Consequently, the applicant used a case-cohort design to sample subjects from the studies, and imputed missing baseline serostatus using an imputation model with covariates and outcome variables. As a supportive analysis, the applicant also imputed serostatus using a Dengue anti-NS1 IgG ELISA (NS1) measured at month 13 (M13). The results of the estimated VE against symptomatic VCD (during active phase)

and risks against HVCD (during entire study period) and SVCD (during entire study period) due to any serotype for children aged 6 to 8 years, using the Immunogenicity Subset (immunoset), the multiple imputation, and the NS1 at M13 are given in the first three rows of Table 1.

Table 1: Estimated risk against symptomatic VCD (during active phase), HVCD (during entire study period) and SVCD (during entire study period) due to any serotype in subjects aged 6 to 8 years classified as seropositive by PRNT50 at M0

Method	**VE Against Symptomatic VCD (CYD14) 95% CI**	**Hazard Ratio against HVCD (CYD14+CYD23/57) 95% CI**	**Hazard Ratio against SVCD (CYD14+CYD23/57) 95% CI**
Immunogenicity subset	67.8 (-11.8,91.7)	0.388 (0.11, 1.28)	0.345 (0.03, 3.01)
Multiple Imputation (MI) of $PRNT_{50}$ at M0	67.3 (39.9, 82.2)	0.262 (0.148, 0.463)	0.321 (0.090, 1.142)
NS1 (Thr9) at M13	55.8 (1.8, 80.1)	0.278 (0.166, 0.468)	0.368 (0.133, 1.019)
Conditional binomial model fit to Immunogenicity Subset with power beta prior*	72.6 (40.9, 88.1)	0.398 (0.173, 0.892)	0.367 (0.081, 1.537)

*The power parameter was estimated using the ratio of cases in the 6-8 age group to the total
Source: Modified from Table 1 in Response to CBER Information Request Dated April 20, 2023

The confidence intervals differ in width due to different numbers of cases/subjects used to estimate the VE and RR. However, the point estimates across different methods are largely consistent. Sample sizes and case counts are presented within the memo when each endpoint is discussed.

Upon evaluation of the multiple imputation (MI) results, the statistical reviewer noted that the overall cross-validated misclassification rate using the MI model for vaccine cases in the immunogenicity set was much higher than for placebo cases (32% versus 13.1%). Furthermore, because the percentage of missing baseline serostatuses was very high, the quality of the imputation of missing values relied heavily on the generalizability of the MI model fitted using the non-missing data from a fraction of the participants (128 subjects aged 6 – 8 years in the extended sub-cohort who were also in the Immunogenicity Subset).

Therefore, the statistical reviewer requested a sensitivity analysis that used the MI model fitted using the sub-cohort to recalculate VE on baseline seropositive subjects in the 6 – 8 age group in the Immunogenicity Subset, employing a leave-one-out imputation of baseline serostatus to evaluate the quality of imputed data based on the MI method. A review of the analysis results revealed a potential for anti-conservative bias in reported VE estimates using the MI approach. Consequently, the statistical reviewer requested that the applicant provide an analysis in the immunogenicity subset that did not impute serostatus at baseline but instead attempted to increase precision in the 6-8 age group in the immunogenicity subset by borrowing information across the 2 – 5 and 9 – 16 age groups in the CYD14 study, which was the only efficacy study that included all three age groups. For the borrowing analysis, exchangeability across age groups was considered

justified according to an internal discussion with the clinical review team because no a priori differences in VE across age groups were anticipated.

The applicant fit a power prior model (Jin, M. et al. (2020) "Bayesian Approaches on Borrowing Historical Data for Vaccine Efficacy Trials". *Statistics in Biopharmaceutical Research* 12: 284-292) where the prior likelihood was constructed using the 2 – 5 and 9 – 16 age groups in CYD14 combined. The power parameter of the prior likelihood was estimated using the ratio of cases in the 6 – 8 age group in CYD14 to that of the total number of cases. Heuristically, this choice of power parameter will discount the other age group information to the extent that there is as much information from the 6 – 8 age group so that the information from the other age groups does not overwhelm posterior inference about the 6 – 8 age group.

The posterior VE estimates and credible intervals reported by the applicant appear in the last row in Table 1. The estimates were similar to alternative Bayesian analyses conducted by the statistical reviewer using the data from study CYD14. Based on internal discussion, the review team agreed that the reported results on the endpoints of VE against symptomatic VCD during the Active Phase, HVCD and SVCD during the entire study period would likely support the effectiveness of Dengvaxia in subjects 6-8 year of age who are seropositive based on the totality of evidence, given that the VE results from various analyses were largely consistent.

For reference, the results from the 9 – 16 age group, fitted using the Immunogenicity Subset and the two main imputations, are presented in Table 2. The results appear consistent across imputation methods and age groups. The magnitudes of the HRs for the safety endpoints are lower overall for the 9 – 16 age group versus the 6 – 8 age group. However, the SVCD case counts were sparse for both age groups, but the estimated HRs in both groups are well below 1.0.

Table 2: Estimated risk against symptomatic VCD (during active phase), HVCD (during entire study period) and SVCD (during entire study period) due to any serotype in subjects aged 9 to 16 years classified as seropositive – CYD14+CYD15+CYD23/57

Method	**VE Against Symptomatic VCD (CYD14) 95% CI**	**Hazard Ratio against HVCD (CYD14+CYD23/57) 95% CI**	**Hazard Ratio against SVCD (CYD14+CYD23/57) 95% CI**
Immunogenicity subset	81.9 (67.2, 90.0)	0.286 (0.12, 0.66)	0.162 (0.0, 2.02)
Multiple Imputation (MI) of $PRNT_{50}$ at M0	77.6 (70.2, 83.2)	0.197 (0.127, 0.306)	0.156 (0.063, 0.391)
NS1 (Thr9) at M13	76.7 (70.2, 81.7)	0.213 (0.151, 0.300)	0.168 (0.082, 0.348)

Source: Reviewer-created table

A caveat to the results reported in the Immunogenicity Subset is that they may be influenced by the earlier recruitment period to be enrolled into the Immunogenicity Subset compared to the entire study recruitment period, despite subjects being randomly selected into the Immunogenicity Subset. However, the time periods were not expected to affect the relative risk of vaccine over placebo, as subjects were randomized to groups and blinding was maintained.

As for safety, an integrated analysis of safety (ISS) performed with updated safety data collected from subjects aged 6 to 8 years in studies CYD14, CYD22, CYD23, CYD24, CYD28, and CYD32 revealed no major new safety issues with this age group from a statistical perspective. I defer to the clinical reviewer for further evaluation of adverse events.

Conclusions

The statistical reviewer ultimately agreed that the totality of primary vaccine efficacy and safety results would likely support the effectiveness and safety of Dengvaxia in seropositive subjects 6-8 years of age. The review team communicated with the applicant to clarify various aspects of the analyses, and requested additional analyses to evaluate the MI prediction of serostatus, and how this affected the robustness of efficacy and safety findings in seropositive individuals. While several potential issues were noted after the applicant was asked to perform sensitivity analyses, alternative analyses conducted by both the applicant and statistical reviewer that were based on an imputation-free approach to avoid the impact of these potential issues were found to be similar to originally reported results on these endpoints.

No major new safety issues with the proposed age group were discovered from a statistical perspective. The reactogenicity profile from the baseline seropositive children aged 6 to 8 years appeared similar to that of children aged 9 to 16 years.

2. CLINICAL AND REGULATORY BACKGROUND

Dengvaxia is currently indicated for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3, and 4 in individuals 9 through 16 years of age living in endemic areas, and is recommended for individuals with prior dengue virus infection. In Europe (Country of Origin), Dengvaxia is indicated for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3, and 4 in individuals 9 to 45 years of age with prior dengue virus infection and living in endemic areas. The current vaccination schedule consists of 3 injections 6-months apart.

Data from 24 clinical studies (5 Phase I studies, 13 Phase II, and 6 Phase III) were used to support the initial marketing authorizations. Three efficacy studies, consisting of 1 proof of concept Phase IIb monocenter study (CYD23, conducted in Thailand) with a long-term safety follow-up phase (CYD57) and 2 pivotal Phase III studies performed in 10 countries of southeast Asia Pacific (CYD14) and Latin America (CYD15) were conducted to demonstrate efficacy of the vaccine.

To support the extension of the indication to include children 6 to 8 years of age, the integrated analyses of safety, immunogenicity, and efficacy were updated with new available data and analysis results, including:

- Final results (long-term follow-up data) of the 2 pivotal efficacy studies CYD14 and CYD15
- Final results of the NS1 Supplemental Analyses used to support the extension of the indication down to children 6 to 8 years of age

Additional studies (CYD65, CYD67, and CYD71), which included subjects aged above 9 years, were used for the comparison of results in subjects aged 6 to 8 years with those in subjects aged 9 years and above.

2.1 Disease or Health-Related Condition(s) Studied

Dengue is an acute, systemic viral infection caused by 4 closely related but antigenically distinct virus serotypes (1, 2, 3, and 4) transmitted primarily by the *Aedes aegypti* mosquito. Half of the world's population is considered at risk of infection by the dengue viruses. Worldwide, an estimated 390 million dengue infections occur every year, of which around 100 million are associated with clinical manifestation of dengue.

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

Besides Dengvaxia, there are no other currently approved vaccinations for the prevention of dengue disease.

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

Dengvaxia is licensed in 21 countries (including the U.S.) and in the European Economic Area (EEA). Efficacy studies conducted in Latin America and Asia Pacific were used to support approval.

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

Please refer to the clinical reviewer’s memo.

2.6 Other Relevant Background Information

None

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

3.1 Submission Quality and Completeness

Submission quality was acceptable to perform a review.

3.2 Compliance With Good Clinical Practices And Data Integrity

Please refer to other disciplines’ reviews.

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

4.1 Chemistry, Manufacturing, and Controls

Please refer to the CMC review memo.

4.2 Assay Validation

The anti-NS1 IgG ELISA was qualified for the original BLA submission. Despite requests by the CBER review team that the applicant update the qualification to a validation, the applicant did not fully comply, but provided updated diagnostic summary statistics on sensitivity and specificity. The CMC and assay reviewers deemed that the assay was acceptable for its intended use.

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

5.1 Review Strategy

This review is based on the applicant's supplement to the BLA submission (STN125682/40) and subsequent amendments to the supplement, in addition to documents from the original BLA (STN125682/0), as necessary to review material in the Supplement. The statistical review focuses on the updated ISS, ISE, NS1 closeout report and the requested analysis based on the immunogenicity subset of CYD14.

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

The following documents were reviewed:

- NS1 Close Out Report
- NS1 Extension Report
- Addendum to Summary of Clinical Safety
- Addendum to Summary of Clinical Efficacy
- Addendum to Clinical Overview
- Amendment 5: Response to CBER Information Request Dated 23 Sept 2022
- Amendment 6: Response to CBER Information Request Dated 6 Oct 2022
- Amendment 8: Response to CBER Information Request Dated 14 Oct 2022
- Amendment 7: Response to CBER Information Request Dated 26 Oct 2022
- Amendment 9: Response to CBER Information Request Dated 12 Dec 2022
- Amendment 10: Response to CBER Information Request Dated 14 Dec 2022
- Amendment 11: Response to CBER Information Request Dated 3 Feb 2023
- Amendment 13: Response to CBER Information Request Dated March 28, 2023
- Amendment 14: Response to CBER Information Request Dated April 20, 2023
- Amendment 14: Response to CBER Information Request Dated April 26, 2023
- Amendment 17: Response to CBER Information Request Dated April 26, 2023

5.3 Table of Studies/Clinical Trials

Studies that were used to support the extension of indication down to 6 – 8 years of age are included in Table 3. Study CYD15 is included because it was used to obtain results in the 9 – 16 years age group as a reference.

Table 3: Studies Included to Support Extended Indication

Study	Objectives, design and schedules	Study Population and # subjects randomized	Conclusions (vaccine efficacy) and lot consistency
CYD14 (Indonesia, Malaysia, Thailand, The Philippines, Viet Nam Endemic areas 03 Jun 2011 to 16 Dec 2013 (Active Phase, 13-month Post-injection 3 follow-up), to 21 Nov 2017 (5-year post-injection 3 follow-up))	Phase III, randomized, placebo controlled, blind-observer, multicenter trial, to evaluate vaccine efficacy (VE) against virologically confirmed dengue post dose 3 cases (Primary endpoint) and safety, including immunogenicity and reactogenicity in a subset of subjects Randomized in two groups: Group 1: CYD dengue vaccine (~5 log10CCID50/serotype 1, 2, 3, 4) at D0, M6 and M12 Group 2: Placebo (NaCl 0 9%) at D0, M6 and M12 0 5 mL/ injection (Subcutaneous) 5-year post-injection 3 follow-up: safety, detection of confirmed hospitalized dengue cases and antibody persistence in a subset of subjects	Healthy Subjects, 2–14 years old Randomized: 10,275 CYD vaccine: 6851 Placebo: 3424	Observed VE point estimate post dose 3 against any serotype was 56 5% (95% CI: 43 8;66 4) with lower bound exceeding the prespecified value of 25% The study reached the primary objective
CYD15 (Brazil, Colombia, Honduras, Mexico, Puerto Rico Endemic areas 08 June 2011 to 03 April 2014 (Active Phase, 13-month post injection 3 follow-up), and to 05 March 2018 (5-year post-injection 3 follow-up))	Phase III, randomized, placebo controlled, blind-observer, multicenter trial, to evaluate vaccine efficacy (VE) against virologically confirmed dengue post dose 3 cases (Primary endpoint) and safety, including immunogenicity and reactogenicity in a subset of subjects Randomized in two groups: Group 1: CYD dengue vaccine (~5 log10CCID50/serotype 1, 2, 3, 4) at D0, M6 and M12 Group 2: Placebo (NaCl 0 9%) at D0, M6 and M12 0 5 mL/ injection (Subcutaneous) 5-year post-injection 3 follow-up: safety, detection of confirmed hospitalized dengue cases and antibody persistence in a subset of subjects	Healthy Subjects, 9–16 years old Randomized: 20,869 CYD vaccine: 13,920 Placebo: 6949	Observed VE point estimate post dose 3 against any serotype was 60 8% (95% CI: 52 0;68 0) with lower bound exceeding the prespecified value of 25% The study reached the primary objective
CYD23 (Thailand, Endemic area, 05 Feb 2009 to 22 Mar 2012 (13 months after injection 3 end of Active phase) End of the study (after a hold): 10 Sep 2013) Long term phase III follow-up of CYD23 subjects after Active Phase (N=3203) (as Study CYD57)	Proof of concept Phase IIb, randomized, controlled, observer-blind, monocenter trial, to evaluate Vaccine efficacy (VE) against virologically confirmed dengue cases and safety Descriptive dengue reactogenicity and humoral immune response, before and after each injection and one year after the 3rd injection, in a subset of subjects Viremia in a subset of subjects Group 1: CYD Dengue Vaccine (~5 log10CCID50/serotype 1, 2, 3, 4) - cohort 1: at D0, M6 and M12 - cohort 2: at D0, M6 and M12 Group 2: - cohort 1: Rabies vaccine (Verorab®) at D0 Placebo (NaCl 0 9%) at M6 and M12 - cohort 2: Placebo at D0, M6 and M12 0 5 mL/ injection Subcutaneous injection	Healthy subjects, 4-11 years old Randomized: 4002 Two-step enrollment as per cohort number: Group 1: 2669 (100 in cohort 1, 2569 in cohort 2) Group 2:1333 (50 in cohort 1, 1283 in cohort 2	Observed VE point estimate post dose3 against any serotype was 30 2% (95% CI: -13 4;56 6) Primary objective was not reached

Source: Table 1 in Summary of Clinical Efficacy

6. Discussion of Analysis Datasets and Approaches

The primary objective of the three efficacy studies (CYD14, CYD15 and CYD23/57) was to assess the efficacy of the CYD dengue vaccine after 3 injections, 6 months apart, in preventing the occurrence of symptomatic VCD cases, regardless of severity, due to any of the 4 serotypes. A symptomatic case was defined as presence of fever (specifically,

≥37.5°C measured at least twice with an interval of at least 4 hours in CYD23 and ≥38°C on at least 2 consecutive days) and laboratory confirmation. Cases occurring more than 28 days after the third injection up to the end of the Active Phase (M13 – M25) were considered for the primary endpoint.

Key additional endpoints included the occurrence of confirmed symptomatic VCD cases by serotype, as well as hospitalized VCD (HVCD) cases and severe VCD (SVCD) cases occurring during the Active Phase as well as the entire study periods.

6.1 Immunogenicity Subset

The CYD dengue vaccine efficacy studies were randomized controlled trials in which subjects were allocated to receive either CYD dengue vaccine or placebo in a 2:1 ratio. In study CYD23, baseline antibody titers were evaluated in blood samples obtained from the first 300 vaccinated subjects. In CYD14 and CYD15, a random subset of subjects (at the beginning of the recruitment periods) provided a pre-vaccination sample (20% and 10% of subjects, respectively). These subjects were designated as the "immunogenicity subset". Subjects in the 3 studies were to receive vaccine or placebo injections at enrollment, M6, and M12. All subjects were to provide a blood sample approximately 28 days after the third injection (M13), although this sample was planned to be tested only in a subset of participants (those in the immunogenicity subset and those subjects developing VCD during follow-up). Baseline dengue seropositivity was defined as a neutralizing Ab level ≥ 10 1/dil against at least one dengue serotype before the first injection, measured by $PRNT_{50}$.

For this submission, immunogenicity of the CYD dengue vaccine according to a 3-dose schedule was assessed in 292 baseline dengue seropositive subjects aged 6 to 8 years, as well as 2544 subjects aged 9 – 16 years, and 373 subjects 2 – 5 years old. See Table 4.

Table 4: Number of seropositive subjects considered for the assessment of immunogenicity

Region	CYD dengue vaccine 2 to 5 years	Control 2 to 5 years	CYD dengue vaccine 6 to 8 years	Control 6 to 8 years	CYD dengue vaccine 9 to 16 years	Control 9 to 16 years
Non-endemic region	-	-	-	-	-	-
Endemic region	373	163	292	152	2544	1005
Endemic Asia Pacific (AP)	334	142	281	136	848	309
Endemic Latin American (LatAm)	39	21	11	16	1696	696

Source: Table 3 in Clinical Overview

Efficacy of the CYD dengue vaccine was assessed in 236 baseline dengue seropositive subjects aged 6 to 8 years (169 subjects in CYD14 and 67 subjects in CYD23) who received the CYD dengue vaccine, and 126 baseline dengue seropositive subjects aged 6 to 8 years (88 subjects in CYD14 and 38 subjects in CYD23) who received the placebo. Table 5 shows the number of seropositive subjects considered for the assessment of efficacy by age group.

Table 5: Number of seropositive subjects considered for the assessment of efficacy (Immunogenicity Subset)

Study	CYD dengue vaccine 2 to 5 years	Placebo 2 to 5 years	CYD dengue vaccine 6 to 8 years	Placebo 6 to 8 years	CYD dengue vaccine 9 to 17 years	Placebo 9 to 17 years	CYD dengue vaccine 6 to 16 years	Placebo 6 to 16 years
CYD23	14	10	67	38	59	21	126	59
CYD14	245	105	169	88	487	251	656	339
CYD15	-	-	-	-	1073	512	1073	512
CYD14 and CYD15	245	105	169	88	1560	763	1729	851

Source: Table 4 in Clinical Overview

The VE and risk estimates for VCD, HVCD, and SVCD in baseline seropositive subjects 6 – 8 years old in the Immunogencitiy Subset are given in Table 6, below.

Table 6: Estimated risk against symptomatic VCD, HVCD and SVCD due to any serotype in subjects aged 6 to 8 years and classified as seropositive by PRNT50 at M0 (Immunogencity Subset)

VE Against Symptomatic VCD (CYD14) 95% CI	Hazard Ratio against HVCD (CYD14+CYD23/57) 95% CI	Hazard Ratio against SVCD (CYD14+CYD23/57) 95% CI
67.8 (-11.8, 91.7)	0.388 (0.11, 1.28)	0.345 (0.03, 3.01)

Source: Reviewer-created table

To improve the precision of vaccine efficacy estimates by including subjects that were not in the immunogenicity subset, a supplemental case-cohort study using an anti-nonstructural protein 1 (NS1) immunoglobulin G (IgG) enzyme-linked immunosorbent assay (ELISA) on samples from the 3 efficacy trials was performed. Dengue anti-NS1 antibodies measured in post-dose 3 (PD3) samples, which were collected in all subjects, were used to impute baseline dengue serostatus and assess the effect of serostatus on vaccine efficacy and long-term safety.

6.2 NS1 Close Out Supplemental Analysis

The NS1 Supplementary Analysis included additional subjects from the CYD14, CYD15, and CYD23/57 studies according to a case-cohort sampling design to obtain efficacy and risk estimates by dengue serostatus. The case-cohort design included a randomly selected "sub-cohort" from the studies, as well as all virologically-confirmed dengue (VCD) cases from M0 until the end of the studies. Cases corresponded to the following 3 endpoints of interest: symptomatic VCD, dengue hospitalizations, and severe dengue. Endpoints were evaluated according to baseline serostatus as determined by baseline (M0) PRNT50, based on either measured or predicted/imputed PRNT serostatus, as described in Section 6.2.2 Design Overview.

6.2.1 Objectives (Primary, Secondary, etc)

The NS1 Supplementary Analyses were done to provide additional evaluation of safety and efficacy by baseline serostatus, using an anti-NS1 IgG ELISA at M13 as a surrogate for baseline serostatus at M0 or an imputed baseline serostatus from a multiple imputation (MI) model. Results from the NS1 Supplementary Analyses were considered supportive for an extended indication for seropositive children down to 6 years of age.

This section reviews the general design of the Supplementary analyses. Results of the analyses are reviewed within Section 7. Integrated Overview of Efficacy. Because the proposed indication is for seropositive children, results for baseline seronegative children are not presented in this memo.

6.2.2 Design Overview

As stated, among all randomized subjects from the 3 efficacy trials (35,146 subjects), serostatus at baseline was known for subjects included in the Immunogenicity Subset. This population represented approximately 7.5%, 10%, and 20% of study participants in CYD23, CYD15, and CYD14, respectively.

Since VE can be directly estimated only among those who were baseline seropositive in the immunogenicity subset, the precision of the estimate was poor due to small sample size. To improve precision of VE estimates by increasing the size of the population assessed, the applicant leveraged a dengue anti-NS1 IgG ELISA to test samples collected at M13. Blood samples from M13 were available from almost all individuals as per study design; however, they could not be analyzed with the traditional PRNT assay used to assess serostatus at baseline because it could not distinguish between vaccination and prior dengue infection.

The NS1 assay was intended to allow differentiating anti-NS1 antibodies induced by wild-type (WT) dengue infection from those induced by vaccination (since the CYD dengue vaccine contains genes encoding NS1 from the yellow fever 17D vaccine virus rather than from dengue virus); therefore, it was used to infer participants' baseline dengue serostatus.

Results from the Immunogenicity Subset include data from all 3 efficacy studies. However, results from the NS1 Supplemental Analyses only include results from the two Phase III efficacy trials (CYD14 and CYD15). CYD23 differed from Phase III efficacy studies, as it was a Proof-of-Concept study with a restricted geographic coverage (mono-centric mono-country study) and with a different algorithm for defining a VCD case. Subjects from CYD23/57 were included in the sub-cohort. However, VCD cases from CYD23/57 were not included in efficacy assessments (e.g., symptomatic VCD during the Active Phase) in the NS1 Supplemental Analyses, due to issues related to patient consent.

Risks of HVCD and SVCD were evaluated according to baseline serostatus as determined by PRNT50 at M0 for the classification of dengue serostatus, which was based on either measured or predicted/imputed PRNT serostatus. All VCD cases which

occurred in CYD14, CYD15, CYD23/57 up to the end of the trial were included (the total duration of the 3 efficacy trials).

These analyses primarily used 2 different approaches to impute baseline serostatus, if not measured:

- Multiple imputation (MI) of PRNT50 at Month 0 (MI PRNT50 M0): PRNT50 results either measured (for subjects included in the Immunogenicity Subset) or predicted based on anti-NS1 values at M13 and covariates such as age, sex, country, and treatment group using a multiple imputation model (for subjects for whom baseline serostatus data were not available)
- Anti-NS1 antibody titer at M13 using a cut-off threshold of ≥ 9 EU/mL (NS1 [Thr9] M13)

As sensitivity analyses, 2 other approaches were used to increase the specificity (to reduce the number of participants wrongly classified as baseline seropositive):

- Multiple imputation of PRNT90 at Month 0 (MI PRNT90 M0)
- Anti-NS1 antibody titer threshold ≥ 50 EU/mL (NS1 [Thr50] M13)

The Case-cohort Design

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 baseline dengue serostatus.

The sub-cohort included a random selection of approximately 10% of the entire study populations of CYD14, CYD15, and CYD23/57 after stratifying by age and trial site. The cases, corresponding to all events of interest (regardless of whether included or not in the sub-cohort), were all symptomatic VCD which occurred in CYD14, CYD15, and CYD23/57 during the Active Phase or in CYD14 and CYD15 during the Surveillance Expansion Period (SEP), and all HVCD and SVCD until the end of each study, depending on the analysis. The case- cohort included individuals from the sub-cohort (with or without VCD cases) plus remaining individuals with VCD events.

Specifically, the sub-cohort consisted of the following:

- CYD14: a random sample of 50% of subjects in the immunogenicity subset, who had a M13 visit and provided PD3 blood samples; this corresponds to approximately 10% of all CYD14 study subjects. The random sampling was stratified by age (2 to 5 years, 6 to 11 years, and 12 to 14 years) and by site, mirroring the stratification used for the generation of the entire immunogenicity subset.
- CYD15: subjects belonging to the immunogenicity subset who had a M13 visit and provided PD3 blood samples; this corresponded to approximately 10% of all CYD15 study subjects.
- CYD23/57: a random sample of 10% of all subjects who consented for participation in study CYD57, and who had a M13 visit and provided PD3 samples in study CYD23. The random sampling was stratified by age (4 to 5 years, 6 to 8 years, and 9 to 11

years) and site.

As a result, a total of 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.

> ***Reviewer comment****: In a case-cohort design, all events/cases are included in analyses, even if they were not initially sampled into the sub-cohort. Although the event rate in each group is overestimated, a weighted Cox regression model that applied sampling weights to subjects can be used to estimate hazard ratios.*

In order to address potential biases from the enrollment period of the immunogenicity subsets in CYD14 and CYD15 being shorter than the enrollment period of the entire corresponding studies (potentially compromising the representativeness of the original sub- cohort), an expanded sub-cohort that sampled from the immunogenicity subsets of CYD14 and CYD15 (representative of subjects enrolled during the immunogenicity subset recruitment period) as well as from the subset of subjects enrolled outside of the CYD14 and CYD15 immunogenicity subset recruitment periods was formed.

In a further expansion, the applicant also included all VCD dengue events occurring *between* M0 and M13 and the classification of their baseline serostatus based on measured PRNT50 (if within the immunogenicity subsets) or imputed/predicted PRNT serostatus (if outside the immunogenicity subset). The expanded sub-cohort targeted a size of 10% of the entire study cohorts.

> ***Reviewer comment****: The CYD23 study assessed baseline serostatus on a non-random sample of 300 subjects (Immunogenicity Subset). These subjects were enrolled during an earlier recruitment period than the remaining subjects. However, the "repair" component of the CYD23 sub-cohort did not address this issue of earlier recruitment as it did for the CYD14 and CYD15 studies.*
>
> *The original sub-cohort and its expanded repair appear to be a reasonable strategy to mimic a post-hoc randomly selected representative sample from the total cohort for later downstream analyses.*

6.2.3 Analysis Population

- For both safety and efficacy analyses, the Full Analysis Set for Efficacy (FASE) from the source studies or subsets of it (by covariates) were used. 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 ("as treated"). For efficacy analyses, subjects were analyzed according to the injection assigned at randomization ("as randomized" or intent-to-treat). The Full Analysis Set for Immunogenicity Subset (FASI) included subjects from the FASE who were also in the Immunogenicity Subset.

- MI $PRNT_{50}$ M0 and MI $PRNT_{90}$ M0 methods included all cases from M0 to M25 during the Active Phase and allowed estimating VE during the whole Active Phase (D0-M25).
- NS1 (Thr9) M13 and NS1 (Thr50) M13 methods estimate VE from post-dose 3 (PD3) until the end of Active Phase (M13-M25) and exclude VCD cases from M0 to M13.

6.2.4 Surveillance/Monitoring

Surveillance activities related to the detection of suspected dengue cases (or suspected dengue hospitalizations) are described in the clinical reviewer's memo.

6.2.5 Endpoints and Criteria for Study Success

The endpoints mentioned in this section were reviewed in this memo. For seropositivity determined by PRNT50 (either measured or imputed), analyses of efficacy endpoints included the period from M0 to M25 (Active Phase), and analyses of safety endpoints included the period from M0 to M72 (Entire Study Period). For seropositivity determined by NS1 threshold at M13, analyses of efficacy and safety endpoints began at M13.

Efficacy analyses of data from the SEP are also briefly discussed in this memo.

Efficacy Endpoint

- Occurrence of symptomatic VCD cases between M0 and the end of the Active Phase, regardless of severity in subjects grouped in age ranges (2 – 5 years, 6 – 8 years, 9 – 16 years) who were classified as seropositive

Safety Endpoints

- Occurrence of dengue hospitalization after M0 or after M13 (including Active and Hospital Phase) in study subjects grouped in age ranges (2 – 5 years, 6 – 8 years, 9 – 16 years) and classified as dengue seropositive

- Occurrence of severe dengue after M0 or after M13 (including Active and Hospital Phase) in study subjects grouped in age ranges (2 – 5 years, 6 – 8 years, 9 – 16 years) and classified as dengue seropositive

6.2.6 Statistical Considerations

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

For efficacy analyses reviewed in this memo, data from M0-M25 were used for the MI approach and data from M13-M25 were used for NS1 at M13 approach. Table 7 shows the number of subjects in the sub-cohort by age group.

Table 7: Number of subjects by age group– Subjects in the sub-cohort

Subject Subset	2 to 5 years CYD dengue vaccine	2 to 5 years Control	6 to 8 years CYD dengue vaccine	6 to 8 years Control	9 to 16 years CYD dengue vaccine	9 to 16 years Control	6 to 16 years CYD dengue vaccine	6 to 16 years Control
Subjects at baseline*	263	126	243	131	1878	937	2121	1068
Subjects at baseline excluding those with VCD between M0 and M13*	257	121	237	125	1861	905	2098	1030
Subjects part of the SEP†	202	94	138	72	1447	712	1585	784
Subjects part of the SEP excluding those with VCD between M0 and M13†	196	90	135	67	1432	686	1567	753

* subjects from CYD14+ CYD15+CYD23
† subjects from CYD14+ CYD15
Source: Table 2.2 Addendum to Summary of Clinical Efficacy

Imputation of Missing Baseline Serostatus

The principal analyses determined serostatus by M0 $PRNT_{50}$. M0 $PRNT_{50}$ serostatus was either measured (for subjects in the immunogenicity subset) or predicted in subjects with missing baseline values. Prediction of M0 $PRNT_{50}$ serostatus was done by a multiple imputation (MI) approach. The accuracy of the MI approach was evaluated using cross-validation (CV) by comparing the predicted baseline $PRNT_{50}$ serostatus with observed baseline $PRNT_{50}$ serostatus in the subset of subjects whose baseline $PRNT_{50}$ serostatus was available.

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 against symptomatic VCD, in the expanded case-cohort. For these complementary analyses, the statistical analyses were conducted with seropositive status defined as M13 anti-NS1 titer $\geq$ 9 EU/mL.

Sensitivity analyses determined serostatus by other approaches ("double seronegative", "strict seropositive", and measured/imputed PRNT90 at M0 classifications).

Multiple imputation (MI) was used to impute missing baseline PRNT50 serostatus for subjects in the case-cohort without PRNT50 result at baseline. A logistic regression with 10 iterations was used to impute missing baseline $PRNT_{50}$ serostatus with baseline serostatus (seronegative or seropositive) as the dependent variable and M13 anti-NS1 titers and other variables as predictors. In each of the 10 iterations, Prentice's weighted Cox regression model was used to estimate the risk and efficacy in the expanded case-

cohort. The model, including the vaccine group as covariate, was used to calculate the hazard ratio (HR) for the primary endpoint. The 95% CI of the HR and p-value associated with a Wald-type test statistic was calculated using the variance estimator by Barlow. Rubin's rule was then used to combine the HRs from the 10 iterations to obtain the final estimate of risk or efficacy.

A cutoff value of 0.5 was used to assign baseline serostatus based on predicted probability from the logistic model.

In the logistic regression model, the following variables were included as independent variables:

- M13 anti-NS1 titers (continuous; log10 transformed)
- vaccine group (binary)
- age (continuous; count and categorical implementations were explored early in the development)
- sex (binary)
- country (categorical)
- indicator of whether subject had VCD between M0 and M13 (binary)
- time between onset of VCD case and M13 sample collection date (continuous; if subject had an event between M0 and M13)
- indicator of whether subject had symptomatic VCD between M0 and end of active phase (binary)
- time from M0 to onset of symptomatic VCD (continuous; if subject had symptomatic VCD between M0 and end of active phase)
- interaction term between “indicator of whether subject had symptomatic VCD between M0 and end of active phase” and treatment arm
- indicator of whether subject had dengue hospitalization and/or severe dengue between M0 and the end of the trial
- time from M0 to onset of dengue hospitalization and/or severe dengue
- interaction term between “indicator of whether subject had dengue hospitalization and/or severe dengue between M0 and cut-off date” and treatment arm
- indicator of whether subject had symptomatic VCD during the SEP (binary)
- time from start of the SEP to onset of symptomatic VCD (continuous; if subject had symptomatic VCD during the SEP)
- interaction term between “indicator of whether subject had symptomatic VCD during the SEP” and treatment arm
- interaction term between treatment arm and M13 anti-NS1 titers (continuous; log10 transformed).

The missing data mechanism was assumed to be missing at random (MAR). According to this assumption, baseline serostatus missingness is not dependent on its value (positive or negative), but on other observed variables. In CYD14 and CYD15, whether or not a subject’s baseline PRNT was measured was determined by his (her) membership of immunogenicity subset, which is independent of the subject’s serostatus.

Reviewer comment*: In general, the multiple imputation method appeared to be a reasonable attempt to handle the missing baseline serostatus, but with the following caveats as noted by the statistical reviewer:*

- *The percentage of missing baseline serostatuses was very high (approximately 65% for subjects aged 6 – 8 years). Therefore, the quality of the imputation of missing values relies heavily on the generalizability of the imputation model fitted using the non-missing data from a fraction of the participants (128 subjects aged 6 – 8 years in the expanded sub-cohort who were also in the Immunogenicity Subset).*

  - *As shown in Section 6.2.8 Evaluation of Imputed Baseline Serostatus, when cross-validated on the Immunogenicity Subset, the overall misclassification rate of the imputation model for vaccine cases (over all ages) was 32% (18/56), but for placebo cases was only 13.1% (11/84). Therefore, the estimates of VE in imputed seropositive subjects may be affected. (The Section mentioned above also assesses misclassification -- that is, seronegative as seropositive and the reverse).*

Considering these issues, CBER requested two sensitivity analyses: one that used the MI model on the Immunogenicity Subset and estimated VE only on that Subset, and another that used the NS1 threshold imputation in place of the MI (with a tipping point analysis that accounted for cases occurring between M0 and M13). The sensitivity analyses are described in Section 7. Integrated Overview of Efficacy. The tipping point analyses are described in Section 7.1.7 Additional Efficacy Issues/Analyses.

In addition, a targeted minimum loss estimation was applied to impute missing baseline serostatus and subsequently estimate VE. The applicant did not ultimately submit results from that method, but indicated that the results were similar to those provided for the MI. In that approach, other representations of age (such as count or categorical) were explored.

6.2.7 Study Population and Disposition

The expanded sub-cohort included 3578 subjects across all studies and included between 8.7% and 10.7% of individual study cohorts. 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.

The number of subjects in the sub-cohort was presented by age group and by study group in Table 7. The number of subjects included in the expanded case-cohort analyses for the different endpoints is presented in Table 8.

Table 8: 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

Source: Table 5.1 in NS1 Close-out Report

The percentages of subjects in the sub-cohort with missing PRNT50 M0 titers were 66.7% (1591/2384) in the CYD Dengue Vaccine Group and was 68.5% (818/1194) for the Placebo Group. Among cases, the percentages of missing data were between 77.4% and 89.7%, depending on the clinical outcome. For 6 – 8 year-olds in the sub-cohort (374 total), 246 were missing PRNT50 titer at M0 (~65%).

Serostatus determined by PRNT50

The serostatus of subjects in the sub-cohort defined by baseline PRNT50, either measured (for subjects included in immunogenicity subset) or imputed (for subjects included in the expanded case-cohort study, but not included in the immunogenicity subset), is presented in Table 9.

Table 9: Dengue serostatus by $PRNT_{50}$ at baseline (measured or imputed) - subjects in sub-cohort

All Studies All subjects	**CYD Vaccine Group n (%)**	**Placebo Group n (%)**	**All Subjects N**
Seropositive	1806.6/2384 (75.8%)	884.1/1194 (74.0%)	2690.7/3578 (75.2%)
Subjects < 9 years old	**CYD Vaccine Group n (%)**	**Placebo Group n (%)**	**All Subjects N**
Seropositive	310.7/506 (61.4%)	155.1/257 (60.4%)	465.8/763 (61.0%)
Subjects >= 9 years old	**CYD Vaccine Group n (%)**	**Placebo Group n (%)**	**All Subjects N**
Seropositive	1495.9/1878 (79.7%)	729/937 (77.8%)	2224.9/2815 (79.0%)
CYD14 All subjects	**CYD Vaccine Group n (%)**	**Placebo Group n (%)**	**All Subjects N**
Seropositive	513.2/731 (70.2%)	261.2/368 (71.0%)	774.4/1099 (70.5%)
CYD15 All subjects	**CYD Vaccine Group n (%)**	**Placebo Group n (%)**	**All Subjects N**
Seropositive	1140.3/1423 (80.1%)	544.2/707 (77.0%)	1684.5/2130 (79.1%)
CYD23/57 All subjects	**CYD Vaccine Group n (%)**	**Placebo Group n (%)**	**All Subjects N**
Seropositive	153.1/230 (66.6%)	78.7/119 (66.1%)	231.8/349 (66.4%)

Source: Table 5.2 in NS1 Close-out Report

The overall percentages of seropositive subjects (based on PRNT50 at M0) were 75.8% (1806.6/2384) of subjects in the CYD Dengue Vaccine Group and 74.0% (884.1/1194) in the Placebo Group. Among subjects aged ≥ 9 years, the percentages of seropositive subjects were 79.7% in the CYD Group and 77.8% in the Placebo Group. The proportions of seropositive subjects ≥ 6 years (not shown in table) were 78.3% in the CYD Group and 76.2% in the Placebo Group.

Serostatus determined by PRNT90

The serostatus of subjects in the sub-cohort defined by baseline PRNT90, either measured (for subjects included in immunogenicity subset) or imputed (for subjects included in the expanded case-cohort study, but not included in the immunogenicity subset), is presented in Table 10.

Table 10: Dengue serostatus by $PRNT_{90}$ at baseline (measured or imputed) - subjects in sub-cohort

All Studies All subjects	**CYD Vaccine Group n (%)**	**Placebo Group n (%)**	**All Subjects N**
Seropositive	1618.1 (67.9%)	826.0 (69.2%)	2444.1 (68.3%)
Subjects < 9 years old	**CYD Vaccine Group n (%)**	**Placebo Group n (%)**	**All Subjects N**
Seropositive	221.3 (43.7%)	123.1 (47.9%)	344.4 (45.1%)
Subjects >= 9 years old	**CYD Vaccine Group n (%)**	**Placebo Group n (%)**	**All Subjects N**
Seropositive	1396.8 (74.4%)	702.9 (75.0%)	2099.7 (74.6%)

CYD14 All subjects	**CYD Vaccine Group n (%)**	**Placebo Group n (%)**	**All Subjects N**
Seropositive	428.7 (58.6%)	233.4 (63.4%)	662.1 (60.2%)
CYD15 All subjects	**CYD Vaccine Group n (%)**	**Placebo Group n (%)**	**All Subjects N**
Seropositive	1076.3 (75.6%)	531.8 (75.2%)	1608.1 (75.5%)
CYD23/57 All subjects	**CYD Vaccine Group n (%)**	**Placebo Group n (%)**	**All Subjects N**
Seropositive	113.1 (49.2%)	60.8 (51.1%)	173.9 (49.8%)

Source: Table 5.3 in NS1 Close-out Report

The proportion of seropositive subjects (based on PRNT90 at M0) of any age was 67.9% in the CYD Vaccine Group and 69.2% in the Placebo Group. The proportions of seropositive subjects aged ≥ 9 years were 74.4% in the CYD Vaccine Group and 75.0% in the Placebo Group. Some differences in seropositivity rates between Vaccine and Placebo groups were observed in subjects aged < 9 years (43.7% versus 47.9%, respectively) and subjects from CYD14 (58.6% versus 63.4%, respectively). The proportions of seropositive subjects aged ≥ 6 years in the CYD vaccine Group and the Placebo Group were 71.9% and 72.4%, respectively.

Serostatus determined using dengue anti-NS1 ELISA

The proportion of subjects classified as seropositive by NS1 at M13 (based on a Threshold of 9 EU/mL) in the entire sub-cohort was 76.6%. In subjects aged ≥ 9 years, the proportions of subjects classified as seropositive in the sub-cohort (excluding subjects with VCD between M0 and M13) were 81.5% and 80.1% in the CYD dengue vaccine and Placebo Groups, respectively. The proportions of seropositive subjects aged ≥ 6 years in the CYD dengue vaccine Group and the Placebo Group were 79.6% and 77.7%, respectively. The overall proportions of seropositive subjects in the CYD Dengue Vaccine Group and in the Placebo Group were 77.4% and 75.1%, respectively.

6.2.7.1 Populations Enrolled/Analyzed

For efficacy analyses, the Full Analysis Set for Efficacy (FASE) from the source studies was utilized. The FASE comprised all subjects who received at least one injection of vaccine or placebo. For efficacy analyses during the SEP, the FAS for the SEP (FASSEP) was utilized. It comprised subjects who received at least one injection, who did not have severe non-compliance to Good Clinical Practice, and who signed the SEP informed consent. For safety analyses, subjects were analyzed according to whether or not they actually received at least 1 injection of CYD dengue vaccine ("as treated"), whereas for efficacy analyses, subjects were analyzed according to the injection assigned at randomization ("as randomized" or intent-to-treat).

6.2.7.1.1 Demographics

Table 11 presents the demographic and baseline characteristics by treatment group for subjects in the sub-cohort.

Table 11: Demographic and baseline characteristics by treatment group - subjects in the sub-cohort

Characteristic	CYD Dengue Vaccine Group (N=2384)	Control Group (N=1194)	All (N=3578)
Sex:: Denominator	2384	1194	3578
Male n (%)	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): Denominator	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: Denominator	2384	1194	3578
<9 years n (%)	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): Denominator	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): Denominator	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
Body mass index (kg/m^2) Denominator	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

Source: Table 5.2 in NS1 Extension Report

Overall, 1869 subjects were female (52.2%) and 1709 subjects were male (47.8%) with a mean age of 10.9 years (standard deviation [SD: 3.31]). The proportion of subjects aged ≥ 9 years was 78.7%. The distribution of males to females, mean age, percentage of

subjects by age group, mean height, mean weight, and body mass index in the sub-cohort were generally comparable between the CYD Dengue Vaccine Group and Control Group.

6.2.8 Evaluation of Imputed Baseline Serostatus

6.2.8.1 Concordance Between $PRNT_{50}$ and Dengue Anti-NS1 ELISA at M0 and at M13

The concordance between the PRNT50 assay and the Dengue anti-NS1 IgG ELISA assay was assessed by Cohen's kappa coefficient. Concordance of the classification of dengue serostatus by the NS1 assay (at M0 and at M13) and by the PRNT assay at baseline was assessed for all subjects from CYD14 and CYD15 who are included in the immunogenicity subsets and for whom there were paired data available. Concordance of the classification of dengue serostatus by the anti-NS1 assay at M13 and by PRNT at M13 was also evaluated for subjects from CYD14 and CYD15 who were included in the case-cohort analysis or in the immunogenicity subsets, had a M13 PRNT result, and received placebo. Cross-tabulations and Cohen's Kappa statistics appear in Table 12 and Table 13.

Table 12: Concordance between PRNT assay (M0) and Dengue anti-NS1 IgG ELISA assay (at M0 with threshold 9 EU/mL) for assessment of dengue serostatus - CYD14 + CYD15 immunogenicity subset

Subset	Classification by NS1 Assay	Classification by PRNT Assay Seropositive	Classification by PRNT Assay Seronegative	Total	Cohen's Kappa Coefficient Statistic	95% CI
All subjects	Seropositive	2641	167	2808	--	--
--	Seronegative	217	874	1091	--	--
--	Total	2858	1041	3899	0.752	(0.729, 0.776)
CYD vaccine group	Seropositive	1761	110	1871	--	--
--	Seronegative	167	569	736	--	--
--	Total	1928	679	2607	0.731	(0.702, 0.761)
Placebo group	Seropositive	880	57	937	--	--
--	Seronegative	50	305	355	--	--
--	Total	930	362	1292	0.793	(0.756, 0.831)

Source: Table 9.8 in NS1 Extension Report

Table 13: Concordance between $PRNT_{50}$ assay (M0) and Dengue anti-NS1 IgG ELISA (at M13 with Threshold 9 EU/mL) for assessment of dengue serostatus - CYD14 + CYD15 immunogenicity subset

Subset	Classification by NS1 Assay	Classification by PRNT Assay Seropositive	Classification by PRNT Assay Seronegative	Total	Cohen's Kappa Coefficient Statistic	95% CI
All subjects	Seropositive	2669	263	2932		
--	Seronegative	180	751	931		
--	Total	2849	1014	3863	0.696	(0.670, 0.722)

CYD vaccine group	Seropositive	1785	192	1977		
--	Seronegative	134	471	605		
--	Total	1919	663	2582	0.659	(0.626, 0.693)
Placebo group	Seropositive	884	71	955		
--	Seronegative	46	280	326		
--	Total	930	351	1281	0.765	(0.725, 0.805)

Source: Table 5.5 in NS1 Extension Report

The overall agreement between the PRNT50 and the M13 anti-NS1 IgG ELISA (Threshold 9 EU/mL) for all subjects in CYD14 and CYD15 was 88.5% (3240/3863) with a kappa coefficient of 0.696 ([95% CI: 0.670, 0.722]). In the CYD Vaccine Group, the concordance was lower (kappa coefficient: 0.659 [95% CI: 0.626, 0.693]) than in the Placebo Group (kappa coefficient: 0.765 [95% CI: 0.725, 0.805]).

Among subjects seronegative by PRNT50 at M0, 25.9% (263/1014) of subjects were classified as seropositive by NS1 at M13. This proportion was greater in the CYD Vaccine Group (29.0% [192/663]) than in the Placebo Group (20.2% [71/351]).

Among subjects seropositive by PRNT50 at M0, 6.3% (180/2849) of subjects were classified as seronegative by NS1 at M13. This proportion was greater in the CYD Vaccine Group (7.0% [134/1919]) than in the Placebo Group (4.9% [46/930]).

> ***Reviewer comment****: Subjects with VCD between M0 and M13 were not excluded from Table 13. Such subjects who were seronegative at M0 would be expected to seroconvert according to NS1 by M13, which may confound the concordance results to some extent. Hence, the M13 NS1 imputation could only be used directly for endpoints measured after M13. The difference in concordance across treatment groups may have illustrated an unanticipated impact of vaccination on NS1 titer at M13 (See Section 6.2.8.2 Impact of CYD Vaccine on anti-NS1 Titers at M13), as the overall agreement between PRNT50 and NS1 at M0 was closer between groups: 89.4% for CYD Vaccine and 91.7% for Placebo (Table 12).*

6.2.8.2 Impact of CYD Vaccine on anti-NS1 Titers at M13

In the immunogenicity subset, an increase in the anti-NS1 GMTs post-injection (M13) from pre-vaccination/injection (M0) was observed in the CYD Dengue Vaccine Group (geometric mean titer ratio [GMTR]: 1.28) compared to the Placebo Group (GMTR: 0.99) in subjects without VCDs. This increase in GMTR was observed in the overall population, regardless of baseline serostatus, i.e. an increase in GMTR in the CYD Dengue Vaccine Group compared to Placebo Group in both seropositive and seronegative (defined by measured PRNT50 at baseline) subjects was observed. The increase in GMTs post-vaccination in the CYD Dengue Vaccine Group was observed in both cases and non-cases with higher GMTRs among cases compared to non-cases for events of dengue hospitalization, severe dengue, and symptomatic VCD during the SEP, but not for events of symptomatic VCD during the Active Phase. No increase in GMTs

was observed in the Placebo Group when stratified by whether subjects were cases or non-cases.

The applicant concluded that the vaccine may have an influence on the anti-NS1 readout, and that this influence likely resulted in differential misclassification between vaccine and placebo groups, with misclassification of samples that otherwise would be classified as "seronegative" as "seropositive" in the vaccine group. If such a misclassification affected cases and non-cases differentially, then VE and risk estimates using the NS1 imputation might be biased.

Serostatus classification by NS1 at M13 for seronegative (by NS1 at M0) subjects in the immunogenicity subset is shown in Table 14. Note that this table excludes subjects with VCD between M0 and M13. Thus, dengue infection (as measured in the studies) did not influence the NS1 titer at M13.

Table 14: Serostatus classification by M13 Dengue anti-NS1 IgG ELISA assay (threshold 9 EU/mL) of subjects classified as seronegative by M0 Dengue anti-NS1 IgG ELISA assay - CYD14 and CYD15 immunogenicity subset (excluding subjects with VCD between M0 and M13)

Subjects Seronegative by NS1 Assay at M0	Seropositive Classification by NS1 Assay at M13	Seronegative Classification by NS1 Assay at M13	Total
Placebo group	39 (11.6%)	298 (88.4%)	337
Vaccine group	139 (19.9%)	560 (80.1%)	699
Subject w/ dengue hospitalization in vaccine group	7 (26.9%)	19 (73.1%)	26
Subject w/o dengue hospitalization in vaccine group	132 (19.6%)	541 (80.4%)	673
Subject w/ dengue hospitalization in placebo group	0 (0.0%)	6 (100.0%)	6
Subject w/o dengue hospitalization in placebo group	39 (11.8%)	292 (88.2%)	331
Subject w/ severe dengue (IDMC) in vaccine group	3 (42.9%)	4 (57.1%)	7
Subject w/o severe dengue (IDMC) in vaccine group	136 (19.7%)	556 (80.3%)	692
Subject w/ severe dengue (IDMC) in placebo group	0 (0.0%)	1 (100.0%)	1
Subject w/o severe dengue (IDMC) in placebo group	39 (11.6%)	297 (88.4%)	336
Subject w/ symptomatic VCD during the Active Phase in vaccine group	1 (7.1%)	13 (92.9%)	14
Subject w/o symptomatic VCD during the Active Phase in vaccine group	138 (20.2%)	546 (79.8%)	684
Subject w/ symptomatic VCD during the Active Phase in placebo group	2 (14.3%)	12 (85.7%)	14
Subject w/o symptomatic VCD during the Active Phase in placebo group	37 (11.4%)	287 (88.6%)	324
Subject w/ symptomatic VCD during the SEP in vaccine group	8 (25.0%)	24 (75.0%)	32
Subject w/o symptomatic VCD during the SEP in vaccine group	122 (20.4%)	476 (79.6%)	598

Subjects Seronegative by NS1 Assay at M0	Seropositive Classification by NS1 Assay at M13	Seronegative Classification by NS1 Assay at M13	Total
Subject w/ symptomatic VCD during the SEP in placebo group	0 (0.0%)	15 (100.0%)	15
Subject w/o symptomatic VCD during the SEP in placebo group	37 (13.0%)	247 (87.0%)	284

Source: Table 5.6 in NS1 Close-out Report

Among subjects classified as seronegative at M0 by anti-NS1, 19.9% were misclassified as seropositive using anti-NS1 readouts at M13 in the CYD Dengue Vaccine Group. This misclassification was higher than that observed in the Placebo Group (11.6%).

The misclassification in the CYD Dengue Vaccine Group was higher among subjects with hospitalized dengue (26.9%) compared to those without hospitalized dengue (19.6%) but lower in subjects with symptomatic VCD (7.1%) compared to those without symptomatic VCD (20.2%) during the Active Phase. It was also higher for severe VCD, but the total number of severe cases was small (n=7).

Serostatus classification by NS1 at M13 for seropositive (according to NS1 at M0) subjects in the immunogenicity subset is shown in Table 15.

Table 15: Serostatus classification by M13 Dengue anti-NS1 IgG ELISA assay (threshold 9 EU/mL) of subjects classified as seropositive by M0 Dengue anti-NS1 IgG ELISA assay - CYD14 and CYD15 immunogenicity subset (excluding subjects with VCD between M0 and 13)

Subjects Seropositive by NS1 Assay at M0	Seropositive by NS1 Assay at M13	Seronegative by NS1 Assay at M13	Total
Placebo group	860 (96.7%)	29 (3.3%)	889
Vaccine group	1770 (97.7%)	42 (2.3%)	1812
Subject w/ dengue hospitalization in vaccine group	14 (93.3%)	1 (6.7%)	15
Subject w/o dengue hospitalization in vaccine group	1756 (97.7%)	41 (2.3%)	1797
Subject w/ dengue hospitalization in placebo group	24 (100.0%)	0 (0.0%)	24
Subject w/o dengue hospitalization in placebo group	836 (96.6%)	29 (3.4%)	865
Subject w/ severe dengue (IDMC) in vaccine group	3 (100.0%)	0 (0.0%)	3
Subject w/o severe dengue (IDMC) in vaccine group	1767 (97.7%)	42 (2.3%)	1809
Subject w/ severe dengue (IDMC) in placebo group	8 (100.0%)	0 (0.0%)	8
Subject w/o severe dengue (IDMC) in placebo group	852 (96.7%)	29 (3.3%)	881
Subject w/ symptomatic VCD in vaccine group during the Active Phase	13 (81.3%)	3 (18.8%)	16
Subject w/o symptomatic VCD in vaccine group during the Active Phase	1757 (97.8%)	39 (2.2%)	1796

Subjects Seropositive by NS1 Assay at M0	Seropositive by NS1 Assay at M13	Seronegative by NS1 Assay at M13	Total
Subject w/ symptomatic VCD in placebo group during the Active Phase	38 (97.4%)	1 (2.6%)	39
Subject w/o symptomatic VCD in placebo group during the Active Phase	822 (96.7%)	28 (3.3%)	850
Subject w/ symptomatic VCD during the SEP in vaccine group	21 (95.5%)	1 (4.5%)	22
Subject w/o symptomatic VCD during the SEP in vaccine group	1558 (97.9%)	33 (2.1%)	1591
Subject w/ symptomatic VCD during the SEP in placebo group	14 (100.0%)	0 (0.0%)	14
Subject w/o symptomatic VCD during the SEP in placebo group	751 (97.3%)	21 (2.7%)	772

Source: Table 5.7 in NS1 Close-out Report

From Table 15, misclassification of seropositive subjects as determined by NS1 from M0 at M13 was similar overall across groups, at about 3%. The only category for which misclassification was relatively higher was subjects in the Vaccine group with symptomatic VCD during the Active Phase (18.8%). Combined with subjects with symptomatic VCD during the SEP, the percentage misclassified was 4/38 = 10.5%, compared to combined subjects without symptomatic VCD (39+33)/(1796+1591) = 2.2%.

> ***Reviewer comment****: The higher observed misclassification rates of seronegative hospitalized and severe cases from baseline seronegative to seropositive in the Vaccine group would potentially increase the case count in the Vaccine group, making a comparison to Placebo more conservative for the benefit-risk assessment in seropositive subjects. Misclassification of baseline seropositive cases as seronegative by the NS1 titer in the Vaccine group would be anti-conservative for assessment of VE due to symptomatic VCD during the Active Phase. Of note, Table 15 includes subjects of all ages in the Immunogenicity Subset. In addition, the corresponding number of cases for which Placebo subjects were misclassified from seropositive to seronegative using NS1 (1 case) was somewhat similar to the ratio of Vaccine to Placebo subjects overall, which might offset the impact of misclassified cases in the CYD group to some extent. Furthermore, the NS1 threshold of 9 EU/mL was one of four different imputation methods for baseline serostatus. The primary imputation method was MI, which is evaluated in the next section.*

6.2.8.3 Cross-validation assessment of performance of imputation methods in predicting the M0 PRNT serostatus

The multiple imputation (MI) method was described in Section 6.2.6 Statistical Considerations. The accuracy of the MI was cross-validated for predictability of actual

baseline PRNT50 serostatus by applying the MI model to the immunogenicity subset of subjects with measured PRNT50 at M0. Table 16 shows the results of the cross validation across all ages and combined over treatment groups.

Table 16: Cross-validation to assess performance of logistic regression used in multiple imputation in predicting M0 PRNT50 serostatus using NS1 M13 titer and other covariates - CYD14 and CYD15 immunogenicity subset

Subset	Predicted Serostatus	Observed Seropositive M0 PRNT50 Serostatus	Observed Seronegative M0 PRNT50 Serostatus	Total
All (immunoset) subjects	Seropositive	2622 (93.9%)	169 (6.1%)	2791
--	Seronegative	227 (21.2%)	845 (78.8%)	1072
All Subjects with VCD between M0 and M13	Seropositive	20 (76.9%)	6 (23.1%)	26
--	Seronegative	9 (30.0%)	21 (70.0%)	30
All Subjects without VCD between M0 and M13	Seropositive	2602 (94.1%)	163 (5.9%)	2765
--	Seronegative	218 (20.9%)	824 (79.1%)	1042

A tenfold cross-validation was run to assess performance of logistic regression used for the MI procedure
Source: Table 5.8 in NS1 Close-out Report

Among all subjects in the immunogenicity subset classified as seronegative by MI, 78.8% were also seronegative by measured $PRNT_{50}$. Among all subjects in the immunogenicity subset classified as seropositive by MI, 93.9% were also observed seropositive by measured $PRNT_{50}$.

In all subjects with events occurring between M0 and M13, 70.0% of subjects predicted to be seronegative were seronegative by measured PRNT50 and 76.9% of subjects predicted to be seropositive were observed seropositive by measured $PRNT_{50}$.

> ***Reviewer comment****: The statistical reviewer computed the following classification statistics based on the table above:*
>
> - *Sensitivity: P(predict sero+| observed sero+) = (2622/2849) = 92%*
> - *Specificity: P(predict sero-| observed sero-) = (845/1014) = 83.3%*
> - *Positive Predictive Value: P(observed sero+| predict sero+) = (2622/2791) = 93.9% . Thus, approximately 6% of those predicted seropositive were seronegative by actual PRNT50 at M0.*
> - *Negative Predictive Value: P(observed sero- | predict sero-) = (845/1072) = 78.8%. Approximately 21% of those predicted seronegative were seropositive by actual PRNT50 at M0.*

CBER requested further granularity of predictive capability by treatment group, and by symptomatic VCD cases. Table 17 shows predicted and observed serostatus in the immunogenicity subset, by several subgroups.

Table 17: Cross-validation to assess performance of logistic regression used in multiple imputation in predicting M0 PRNT50 serostatus using M13 NS1 titer and other covariates - CYD14 and CYD15 immunogenicity subset

Subset	Predicted Serostatus	PRNT50 Seropositive	PRNT50 Seronegative	Total
All subjects	Seropositive	2622 (93.9%)	169 (6.1%)	2791
--	Seronegative	227 (21.2%)	845 (78.8%)	1072
All Subjects with VCD between M0 and M13	Seropositive	20 (76.9%)	6 (23.1%)	26
--	Seronegative	9 (30.0%)	21 (70.0%)	30
All Subjects w/o VCD between M0 and M13	Seropositive	2602 (94.1%)	163 (5.9%)	2765
--	Seronegative	218 (20.9%)	824 (79.1%)	1042
Placebo subjects	Seropositive	872 (95.2%)	44 (4.8%)	916
--	Seronegative	58 (15.9%)	307 (84.1%)	365
Placebo Subjects with VCD between M0 and M13	Seropositive	15 (83.3%)	3 (16.7%)	18
--	Seronegative	3 (25.0%)	9 (75.0%)	12
Placebo Subjects w/o VCD between M0 and M13	Seropositive	857 (95.4%)	41 (4.6%)	898
--	Seronegative	55 (15.6%)	298 (84.4%)	353
Vaccine subjects	Seropositive	1750 (93.3%)	125 (6.7%)	1875
--	Seronegative	169 (23.9%)	538 (76.1%)	707
Vaccine Subjects with VCD between M0 and M13	Seropositive	5 (62.5%)	3 (37.5%)	8
--	Seronegative	6 (33.3%)	12 (66.7%)	18
Vaccine Subjects w/o VCD between M0 and M13	Seropositive	1745 (93.5%)	122 (6.5%)	1867
--	Seronegative	163 (23.7%)	526 (76.3%)	689
Subjects with symptomatic VCD after M0	Seropositive	67 (83.8%)	13 (16.3%)	80
--	Seronegative	16 (26.7%)	44 (73.3%)	60
Subjects w/o symptomatic VCD after M0	Seropositive	2555 (94.2%)	156 (5.8%)	2711
--	Seronegative	211 (20.8%)	801 (79.2%)	1012
Placebo subjects with symptomatic VCD after M0	Seropositive	53 (89.8%)	6 (10.2%)	59
--	Seronegative	5 (20.0%)	20 (80.0%)	25
Placebo subjects w/o symptomatic VCD after M0	Seropositive	819 (95.6%)	38 (4.4%)	857
--	Seronegative	53 (15.6%)	287 (84.4%)	340
Vaccine subjects with symptomatic VCD after M0	Seropositive	14 (66.7%)	7 (33.3%)	21
--	Seronegative	11 (31.4%)	24 (68.6%)	35
Vaccine subjects w/o symptomatic VCD after M0	Seropositive	1736 (93.6%)	118 (6.4%)	1854
--	Seronegative	158 (23.5%)	514 (76.5%)	672

Source: Table 9.1.11a in Response to CBER IR December 12, 2022

According to Table 17, the overall accuracy of classification for Vaccine subjects with VCD (i.e., cases) was relatively low compared to Placebo subjects with VCD and to Vaccine subjects without VCD. The overall cross-validation (CV) misclassification rate using the MI model for vaccine subjects with symptomatic VCD after M0 in the immunogenicity set was 32% (18/56) versus 13.1% (11/84) for placebo subjects with symptomatic VCD after M0. The statistical reviewer noted the following:

- For Vaccine cases, 33.3% (7/21) of those predicted seropositive were seronegative based on observed PRNT50.
  - For efficacy analyses, this may be conservative because it increases the vaccine case count in the seropositive category, making the vaccine efficacy underestimated.
  - 31% (11/35) of cases predicted seronegative were seropositive based on observed PRNT50. This may be anti-conservative because it removes vaccine cases from

the seropositive group.

- For Placebo cases, 10.2% (6/59) of those predicted seropositive were seronegative based on observed PRNT50.
  - For efficacy analyses, this may be anti-conservative because it adds placebo cases to the seropositive group.
  - 20% (5/25) of cases predicted seronegative were seropositive based on observed PRNT50. This may be conservative because it removes placebo cases from the seropositive group.

Reviewer comment*: To put the above notes in perspective, consider that what may be anti-conservative for vaccine cases is to move seropositive cases into the seronegative category. Out of the actual 25 seropositive cases in the Vaccine group, 44% (11/25) were moved in the anti-conservative direction by the MI model. However, 22.5% of the actual 31 seronegative cases (7/31) were moved in the conservative direction. This resulted in a net "movement" of around 7% of cases toward the anti-conservative direction.*

What may be anti-conservative for placebo cases is to move seronegative cases into the seropositive category. Out of the actual 26 seronegative placebo cases, 23% (6/26) were moved in the anti-conservative direction by the MI model. However, 8.6% of the actual 58 seropositive cases (5/58) were moved in the conservative direction. This resulted in a net movement of around 1.2% toward the anti-conservative direction.

Further discussion of the MI and its predictions occurs in Section 7.1.4 Analysis of Primary Endpoint.

7. INTEGRATED OVERVIEW OF EFFICACY

The CYD dengue vaccine development program included 2 pivotal large-scale placebo-controlled Phase III efficacy studies, CYD14 (N=10,275) and CYD15 (N=20,869), conducted in endemic countries among children 2 to 14 years and 9 to 16 years, respectively. Both studies lasted approximately 6 years including an active surveillance phase (from M0 to M25) to mainly assess vaccine efficacy (VE) and a hospital phase (M25 to M72), for detection of hospitalized cases with follow-up for an additional 4 years. An active surveillance system ("surveillance expansion phase" [SEP]) was reinstituted in both studies after the detection of a safety signal in study CYD14 to better monitor VE and safety, covering approximately the last 2 years of the planned follow-up period.

Study CYD23 was a Phase IIb efficacy study conducted in Thailand among children 4 to 11 years with a similar study design; Active surveillance (Active Phase) was performed during the first 2 years of the study. Subjects from study CYD23 were then followed in a hospital surveillance in CYD57 for 4 years. however, no SEP was instituted as this study was completed at the time the safety signal in study CYD14 was detected.

Prior exposure to wild-type dengue infection was identified as an important covariate for efficacy in the CYD14 and CYD15 trials. In a subset of subjects for whom serostatus at baseline was evaluated (designated as the "immunogenicity-subset"), efficacy was higher in those previously exposed to dengue (referred to as "seropositive" and defined as plaque reduction neutralization test (PRNT) ≥ 1:10 to any dengue serotype at baseline) than in those who were dengue-naïve at baseline (referred to as "seronegative"). Pooled VE against VCD cases in subjects aged ≥ 9 years at enrollment participating in the 2 Phase III pivotal efficacy studies was 52.5% (95% CI: 5.9; 76.1) among subjects classified as seronegative at baseline. In contrast, the pooled VE against VCD cases across these 2 pivotal efficacy studies was 81.9% (95% CI: 67.2; 90.0) among subjects ≥ 9 years of age classified as seropositive at baseline.

In these 3 efficacy studies, dengue baseline serostatus was assessed in an Immunogenicity Subset corresponding to approximately 7.5%, 10%, and 20% of study participants in CYD23, CYD15, and CYD14, respectively.

7.1 Indication #1: Extension of the Age Indication Down to Children 6 to 8 Years of Age with Prior Dengue Virus Infection and Living in Endemic Areas

7.1.1 Methods of Integration

In the original BLA, an analysis that pooled the results of the efficacy studies (CYD14 + CYD15) estimated VE against symptomatic VCD, HVCD, and SVCD over a 25-month period in individuals 9-16 years of age. These results were updated with final data of the CYD14 and CYD15 studies, along with new analyses to impute the dengue serostatus at baseline (NS1 Supplemental Analyses). Pooled analyses were performed to improve precision of estimates for specific endpoints such as VE by serotype and VE against HVCD and SVCD cases (the latter two incorporated CYD23/57 as well).

In addition to analyses that support an extension to seropositive children 6 to 8 years old, analyses on seropositive subjects aged 9 to 16 years are presented as a benchmark, and on seropositive subjects aged 2 to 5 years to provide perspective in a younger age group.

Person-time at risk

'Person-time at risk' was the cumulative time (in days) until a subject was diagnosed with VCD or at risk to develop a VCD, whichever came first. Specifically,

- If a subject had VCD in the considered period, the person-time at risk was equal to the time to onset of dengue.
- If a subject did not contract VCD in the considered period, the person-time at risk was equal to the duration of the surveillance.

VE Calculation for analysis of individual studies

$VE = 100* [1- (P_{CYD} / P_P)] = 100* [1-((C_{CYD} / N_{CYD}) / (C_P / N_P))]$

where:

P_{CYD} is the incidence rate of dengue in the CYD dengue vaccine Group;

P_P is the incidence rate of dengue in the Control Group;

C_{CYD} is the number of VCD cases in the CYD dengue vaccine Group;

N_{CYD} is the total person-year in the CYD dengue vaccine Group;

C_P is the number of VCD cases in the Control Group;

N_P is the total person-years in the Control Group.

Person-years was calculated as the sum of individual units of time (years) for which the subjects contributed to the analysis, and is equal to the person-time at risk (days) divided by 365.25.

For subjects with several episodes of dengue, only the first episode of VCD occurring more than 28 days after the third injection was included in the analysis of VE.

VE Calculation for analysis of pooled studies

VE = 100* [1- (Hazard Ratio)]

The hazard ratio was obtained using a Cox regression model which included treatment group, study and study-by-group interactions as fixed effects.

7.1.2 Demographics and Baseline Characteristics

The demographic characteristics of baseline seropositive subjects aged 6 to 8 years and 9 to 16 years included in the Immunogenicity Subset for the Active Phase and the SEP are presented in Table 18.

Table 18: Demographics at baseline – Seropositive subjects aged 6 to 8 and 9 to 16 years – Efficacy analysis sets

Analysis Set	Studies	6 – 8 years CYD dengue Male n (%)	6 – 8 years CYD dengue Mean Age	6 – 8 years Control Male n (%)	6 – 8 years Control Mean Age	9 – 16 years CYD dengue Male n (%)	9 – 16 years CYD dengue Mean Age	9 – 16 years Control Male n (%)	9 – 16 years Control Mean Age
FASI	**CYD14**	82/236 (48.5)	7.5	46/126 (52.3)	7.4	245/1619 (50.3)	12.3	122/784 (48.6)	12.2
	CYD15	--	--	--	--	512/1619 (47.7)	12.4	272/784 (53.1)	12.5
	CYD14+CYD15	--	--	--	--	757/1619 (48.5)	12.4	394/784 (51.6)	12.4
	CYD23	27/236 (40.3)	7.7	17/126 (44.7)	7.7	28/1619 (47.5)	10.0	8/784 (38.1)	10.2
	CYD14+CYD15 +CYD23	109/236 (46.2)	7.5	63/126 (50.0)	7.5	785/1619 (48.5)	12.3	402/784 (51.3)	12.4
FASSEP	**CYD14**	81/167 (48.5)	7.5	45/85 (52.9)	7.4	228/1335 (50.6)	12.3	115/653 (48.1)	12.2
	CYD15	--	--	--	--	411/1335 (46.5)	12.4	221/653 (53.4)	12.5
	CYD14+CYD15	--	--	--	--	639/1335 (47.9)	12.3	336/653 (51.5)	12.4

Source: Modified from Table 2.1 in Addendum to Section 2.7.3 Summary of Clinical Efficacy

7.1.4 Analysis of Primary Endpoints

The FAS for the Immunogenicity Subset (FASI) was defined as all subjects who received at least one injection of the CYD dengue vaccine or control vaccine, and who had at least 1 blood sample drawn and 1 valid post-injection serology result (i.e., a result different from "not-reportable" or missing, for at least 1 dengue serotype). The FASI was used for efficacy analyses that used only the Immunogenicity Subset in the ISE.

Primary Objectives

For efficacy in baseline dengue seropositive subjects aged 9 to 16 years, 6 to 8 years, and 6 to 16 years during the Active Phase, the objectives were

- To describe efficacy of the CYD dengue vaccine in preventing the occurrence of VCD cases due to any serotype during the Active Phase (D0-M25).
- To describe efficacy of the CYD dengue vaccine in preventing the occurrence of VCD cases due to each serotype during the Active Phase (D0-M25).
- To describe efficacy of the CYD dengue vaccine during the Active Phase (D0-M25) in preventing:
  - HVCD due to any serotype.
  - SVCD (as per IDMC definition) due to any serotype.

For efficacy in baseline dengue seropositive subjects aged 9 to 16 years, 6 to 8 years, and 6 to 16 years during the Surveillance Expansion Phase (SEP), the objectives were

- To describe efficacy of the CYD dengue vaccine in preventing the occurrence of VCD cases due to any serotype during the SEP.
- To describe efficacy of the CYD dengue vaccine in preventing the occurrence of VCD cases due to each serotype during the SEP.
- To describe efficacy of the CYD dengue vaccine during the SEP in preventing:
  - HVCD due to any serotype.
  - SVCD (as per IDMC definition) due to any serotype.

Efficacy endpoints measured only during the SEP are not discussed in this memo. See the clinical reviewer's memo for more details. However, analyses of HVCD and SVCD during the entire study period (including the Active Phase and SEP) are discussed.

Analyses of HVCD and SVCD using only the Active Phase are also not discussed due to the limited number of cases in the 6 – 8 age group during this period from the Immunogenicity Subset (1 in the Vaccine group, and 5 in the Placebo group for HVCD, and 1 Placebo case for SVCD). In addition, the entire study period was the main focus of review for these two endpoints.

Baseline dengue serostatus was determined with 2 approaches: using baseline specimens from subjects participating in the Immunogenicity Subset and based on the NS1

Supplemental Analyses. Section 6.2 NS1 Close Out Supplemental Analysis discusses the case-cohort design used in the imputation of missing baseline serostatus. This memo focuses on analyses that used the two main imputation methods mentioned in that section.

VE against Symptomatic VCD due to any serotype

Immunogenicity Subset Results

In the Immunogenicity Subset, VE against symptomatic VCD due to any serotype during the Active Phase (D0-M25) in baseline seropositive subjects aged 6 to 8 years in study CYD14 was estimated as 67.8% (95% CI: [-11.8%, 91.7%]). When CYD14 and CYD23 are pooled together, VE against VCD due to any serotype is 71.6% with 95% CI (28.9, 88.7). See Table 19.

Table 19: VE against VCD due to any serotype during the Active Phase in baseline seropositive subjects aged 6 to 8 - FASI

Studies	Parameter	6 – 8 years CYD Vaccine Group	6 – 8 years Placebo Group	2 – 5 years CYD Vaccine Group	2 – 5 years Placebo Group
CYD14+CYD23	**Vaccine Efficacy (95% CI)**	--	71.6 (28.9; 88.7)	--	71.6 (20.3; 89.9)
--	**Scaled Schoenfeld residuals p-value**	--	0. 3241	--	0.1119
CYD14	**Number of subjects**	169	88	245	105
--	**n Cases (n episodes)**	5 (5)	8 (8)	6 (6)	9 (10)
--	**Number of person-years at risk**	339	175	492	209
--	**Density incidence (95% CI)**	1.5 (0.5; 3.4)	4.6 (2.0; 8.8)	1.2 (0.4; 2.6)	4.3 (2.0; 8.0)
--	**Vaccine Efficacy (95% CI)**	--	67.8 (-11.8; 91.7)	--	71.6 (10.7; 91.7
CYD23	**Number of subjects**	67	38	14	10
--	**n Cases (n episodes)**	2 (2)	5 (5)	0 (0)	0 (0)
--	**Number of person-years at risk**	131	73	28	18
--	**Density incidence (95% CI)**	1.5 (0.2; 5.4)	6.9 (2.3; 15.3)	0.0 (0.0; 12.2)	0.0 (0.0; 18.9)
--	**Vaccine Efficacy (95% CI)**	--	77.9 (-35.2; 97.9)	--	NC (NC)

n cases: number of subjects with at least one symptomatic virologically-confirmed dengue episode in the considered period n episodes: number of symptomatic virologically-confirmed dengue episodes in the considered period
Density incidence: data are cases per 100 person-years at risk
CIs for the single proportion are calculated using the exact binomial method (Clopper-Person method, quoted by Newcombe)
CIs for VE on individual studies are calculated using the Exact method described by Breslow & Day
Integrated Vaccine Efficacy and CIs are calculated using Cox regression model
Source: Table 2.5 in Summary of Clinical Efficacy

In comparison, VE estimates were higher in older children aged 9 to 16 years and similar in younger subjects aged 2 to 5 years (Table 20 and Table 19, respectively). For seropositive subjects aged 6 to 16 years (CYD14+CYD15), VE was 79.7% with 95% CI (65.7, 87.9). See Table 21.

Table 20: VE against VCD due to any serotype during the Active Phase in baseline seropositive subjects aged 9 to 16 years - FASI

Studies	Parameter	CYD Vaccine Group	Placebo Group
CYD14+CYD15+CYD23	**Vaccine Efficacy (95% CI)**	--	81.9 (67.2; 90.0)
--	**Scaled Schoenfeld residuals p-value**	--	0.9642
CYD14+CYD15	**Vaccine Efficacy (95% CI)**	--	81.9 (67.2; 90.0)
--	**Scaled Schoenfeld residuals p-value**	--	0.9642
CYD14	**Number of subjects**	487	251
--	**n Cases (n episodes)**	7 (7)	17 (18)
--	**Number of person-years at risk**	981	496
--	**Density incidence (95% CI)**	0.7 (0.3; 1.5)	3.4 (2.0; 5.4)
--	**Vaccine Efficacy (95% CI)**	--	79.2 (47.2; 92.7)
CYD15	**Number of subjects**	1073	512
--	**n Cases (n episodes)**	8 (8)	23 (23)
--	**Number of person-years at risk**	2116	994
--	**Density incidence (95% CI)**	0.4 (0.2; 0.7)	2.3 (1.5; 3.5)
--	**Vaccine Efficacy (95% CI)**	--	83.7 (62.2; 93.7)
CYD23/57	**Number of subjects**	59	21
--	**n Cases (n episodes)**	0 (0)	0 (0)
--	**Number of person-years at risk**	117	42
--	**Density incidence (95% CI)**	0.0 (0.0; 3.1)	0.0 (0.0; 8.5)
--	**Vaccine Efficacy (95% CI)**	--	NC (NC)

n cases: number of subjects with at least one symptomatic virologically-confirmed dengue episode in the considered period n episodes: number of symptomatic virologically-confirmed dengue episodes in the considered period
Density incidence: data are cases per 100 person-years at risk
CIs for the single proportions are calculated using the exact binomial method (Clopper-Person method)
CIs for VE on individual studies are calculated using the Exact method described by Breslow & Day
Integrated Vaccine Efficacy and CIs are calculated using Cox regression model
Source: Table 2.3 in Summary of Clinical Efficacy

VE against VCD due to any serotype during the Active Phase in baseline dengue seropositive subjects aged 6 to 16 years is presented in Table 21.

Table 21: VE against VCD due to any serotype during the Active Phase in baseline seropositive subjects aged 6 to 16 years – FASI

Studies	Parameter	CYD Vaccine Group	Placebo Group
CYD14+CYD15+CYD23	**Vaccine Efficacy (95% CI)**	--	79.9 (66.9; 87.7)
--	**Scaled Schoenfeld residuals p-value**	--	0.5353
CYD14+CYD15	**Vaccine Efficacy (95% CI)**	--	79.7 (65.7; 87.9)
--	**Scaled Schoenfeld residuals p-value**	--	0.5185
CYD14	**Number of subjects**	656	339
--	**n Cases (n episodes)**	12 (12)	25 (26)
--	**Number of person-years at risk**	1320	671
--	**Density incidence (95% CI)**	0.9 (0.5; 1.6)	3.7 (2.4; 5.5)

Studies	Parameter	CYD Vaccine Group	Placebo Group
--	**Vaccine Efficacy (95% CI)**	--	75.6 (49.6; 88.8)
CYD15	**Number of subjects**	1073	512
--	**n Cases (n episodes)**	8 (8)	23 (23)
--	**Number of person-years at risk**	2116	994
--	**Density incidence (95% CI)**	0.4 (0.2; 0.7)	2.3 (1.5; 3.5)
--	**Vaccine Efficacy (95% CI)**		83.7 (62.2; 93.7)
CYD23	**Number of subjects**	126	59
--	**n Cases (n episodes)**	2 (2)	5 (5)
--	**Number of person-years at risk**	248	114
-	**Density incidence (95% CI)**	0.8 (0.1; 2.9)	4.4 (1.4; 9.9)
--	**Vaccine Efficacy (95% CI)**	--	81.6 (-12.6; 98.2)

n cases: number of subjects with at least one symptomatic virologically-confirmed dengue episode in the considered period n episodes: number of symptomatic virologically-confirmed dengue episodes in the considered period
Density incidence: data are cases per 100 person-years at risk
CIs for the single proportions are calculated using the exact binomial method (Clopper-Person method, quoted by Newcombe)
CIs for VE on individual studies are calculated using the Exact method described by Breslow & Day
Integrated Vaccine Efficacy and CIs are calculated using Cox regression model
Source: Table 2.7 in Addendum to Summary of Clinical Efficacy

NS1 Supplemental Analysis Results

The NS1 Supplemental Analyses used the sub-cohort and the imputation methods. The estimated efficacy against symptomatic VCD due to any serotype in subjects aged 6 to 8 and 2 to 5 years classified as dengue seropositive was evaluated during the Active Phase (M0-M25 for MI approaches and PD3-M25 for NS1 approaches), and is presented in Table 22. VE in subjects aged 6 to 8 years old with the MI $PRNT_{50}$ M0 approach was 67.3%. In comparison, VE estimates in older children aged 9 to 16 years tended to be higher (around 78%), as shown in Table 23. In younger subjects aged 2 to 5 years, VE estimates tended to be lower for the MI PRNT approaches, and higher for the NS1 approaches than those observed in subjects aged 6 to 8 years.

Table 22: VE against Symptomatic VCD due to any serotype during the Active Phase in subjects aged 6 to 8 and 2 to 5 years classified as seropositive - NS1 Supplemental Analyses (CYD14)

Age Group	Method	CYD Vaccine Group Cases n (N)	Placebo Group Cases n (N)	Vaccine Efficacy	95% CI
6 to 8 years	MI $PRNT_{50}$ M0	35.6 (99.2)	55.4 (51.8)	67.3	(39.9, 82.2)
6 to 8 years	MI $PRNT_{90}$ M0	28.9 (82.5)	46.2 (45.7)	66.3	(38.3, 81.6)
6 to 8 years	NS1 (Thr9) M13	14 (90)	15 (44)	55.8	(1.8, 80.1)
6 to 8 years	NS1 (Thr50) M13	12 (76)	13 (34)	60.5	(6.2, 83.4)

Age Group	Method	CYD Vaccine Group Cases n (N)	Placebo Group Cases n (N)	Vaccine Efficacy	95% CI
2 to 5 years	MI $PRNT_{50}$ M0	45.7 (120.1)	48.9 (57.6)	57.1	(21.6, 76.5)
2 to 5 years	MI $PRNT_{90}$ M0	27.8 (75.9)	35 (43.1)	57.2	(19.0, 77.4)
2 to 5 years	NS1 (Thr9) M13	16 (119)	27 (47)	77.1	(54.6, 88.4)
2 to 5 years	NS1 (Thr50) M13	7 (72)	12 (35)	74.0	(31.6, 90.1)

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: Table 2.6 in Summary of Clinical Efficacy

Table 23: VE against VCD due to any serotype during the Active Phase in subjects aged 9 to 16 years classified as seropositive - NS1 Supplemental Analyses

	CYD Vaccine Group Cases n (N)	Placebo Group Cases n (N)	Vaccine Efficacy Against Symptomatic VCD	95% CI
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 (Thr9) M13	111 (1389)	222 (656)	76.7	(70.2, 81.7)
NS1 (Thr50) M13	79 (1249)	160 (565)	77.9	(70.6, 83.4)
CYD14 MI $PRNT_{50}$ M0	49.6 (293.9)	103.3 (151.8)	76.1	(62.6, 84.8)
MI $PRNT_{90}$ M0	40.7 (270.3)	92.5 (144.6)	77.2	(64.3, 85.4)
NS1 (Thr9) M13	23 (283)	43 (137)	74.1	(55.7, 84.9)
NS1 (Thr50) M13	17 (262)	31 (114)	75.7	(54.9, 86.9)
CYD15 MI $PRNT_{50}$ M0	127.4 (1139.9)	268.2 (544.6)	78.1	(69.9, 84.1)
MI $PRNT_{90}$ M0	107.3 (1076.8)	249.2 (531.3)	79.5	(73.0, 84.5)
NS1 (Thr9) M13	88 (1106)	179 (519)	77.2	(70.1, 82.7)
NS1 (Thr50) M13	62 (987)	129 (451)	78.4	(70.2, 84.3)

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: Table 2.4 in Summary of Clinical Efficacy

Considering the concerns with the imputation that were mentioned in Section 6.2.8 Evaluation of Imputed Baseline Serostatus, CBER sent an IR to the applicant requesting a sensitivity analysis that evaluated the MI model for imputing baseline serostatus on sub-cohort subjects who were in the immunogenicity subset (where baseline serostatus was known). Specifically, CBER requested that the applicant re-calculate VE by age group (6 – 8 years, 9 – 16 years) using only subjects in the immunogenicity subset, by baseline

serostatus. The serostatus for each subject was multiply imputed in a leave-one-out manner in the MI model. The resulting average VE estimate and 95% CI was compared to the VE estimate obtained from the MI model in Table 22, above.

Table 24 compares the two VE estimates for the 6–8 years age group who were baseline seropositive (by imputation or by actual M0 PRNT50). Table 25 shows the same results for the 9 – 16 years age group. In order to eliminate the confounding effect introduced by different studies for the comparison across age groups, results using only study CYD14 are shown for the 9 – 16 year olds because study CYD15 included subjects 9-16 years of age only.

Table 24: VE against Symptomatic VCD - Immunogenicity Set (6-8 years old) seropositive (CYD-14)

--	**Serostatus by actual M0 PRNT50**	**Serostatus by MI model**
VE (95% CI)	67.8 (-11.8, 91.7)	84.6 (11.4, 97.3)
Vaccine Cases	5	3.6*
Placebo Cases	8	8.5*

*Average number over the multiple imputations
Source: Reviewer-created table using information from Response to CBER IR Dated 14 Oct 2022

Table 25: VE against Symptomatic VCD - Immunogenicity Set (9-16 years old) seropositive (CYD-14 only)

--	**Serostatus by actual M0 PRNT50**	**Serostatus by MI model**
VE (95% CI)	79.2 (47.2, 92.7)	83.5 (50.9, 94.4)
Vaccine Cases	7	5.5*
Placebo Cases	17	15.5*

*Average number over the multiple imputations
Source: Reviewer-created table using information from Response to CBER IR Dated 14 Oct 2022

From Table 24, MI classifications of serostatus in the 6-8 age group appeared to underestimate on average the number of cases in the vaccine seropositive group and overestimate the number of cases in placebo seropositive group, resulting in an VE estimate against symptomatic VCD of 84.6% that is much higher than that reported using the Immunogenicity Subset based on actual M0 PRNT50 (67.8%). Similar (although less pronounced) differential predictions of serostatus of vaccine cases versus placebo cases occurred with hospitalized VCD and severe VCD (discussed later). In contrast, such a pattern did not appear with the same analysis performed using the 9-16 age group (Table 25).

> ***Reviewer comment****: Based on the sensitivity analysis results, it was not clear whether the observed discrepancy in designation of serostatus was primarily due*

to chance because of the smaller sample size and case count in the 6-8 age group compared to 9-16 age group, or whether it indicated an actual bias from the MI model predictions. The implication of an actual bias was that the MI model estimates that imputed serostatus for the full subcohort of 6-8 years old subjects in the NS1 Closeout Report were biased too high compared to the estimates that determined serostatus by actual PRNT50 at M0.

The statistical reviewer requested that the applicant provide an analysis that did not impute serostatus at baseline but instead attempted to increase precision in the 6-8 age group in the immunogenicity subset by borrowing information across the 2 – 5 and 9 – 16 age groups in the CYD14 study, since CYD14 is the only Phase 3 study that recruited subjects in all three age groups. Based on internal discussions with the clinical reviewer, exchangeability across age groups was considered justified because no a priori differences in VE across age groups were anticipated.

The applicant adopted a Bayesian approach with a power prior where information from other age groups (2-5 years and 9-16 years) was used to construct the power prior distribution. The methodology described in Jin, M. et al. (2020) "Bayesian Approaches on Borrowing Historical Data for Vaccine Efficacy Trials", Statistics in Biopharmaceutical Research 12: 284-292 was used. The power parameter was estimated by the ratio of cases in the 6 – 8 age group over the total number of cases. Heuristically, this choice of power parameter discounts the information in other age group to the extent that there is as much information from the 6 – 8 age group (in the form of cases compared to the total number of cases) so that the information from the other age groups does not overwhelm posterior inference about the 6 – 8 age group. The resulting posterior mean of VE was 72.6% with a 95% credible interval of (40.9%, 88.1%). The results are summarized in Table 26. The remaining columns in the table regarding risks of HVCD and SVCD are discussed later.

Table 26: Estimated risk against symptomatic VCD (during active phase), HVCD (during entire study period) and SVCD (during entire study period) due to any serotype in subjects aged 6 to 8 years classified as seropositive – CYD14

Conditional binomial model with power beta prior*	VE Against Symptomatic VCD	Risk Against HVCD	Risk Against SVCD
Estimate	VE = 72.6	HR = 0.398	HR = 0.367
95% CI	(40.9, 88.1)	(0.173, 0.892)	(0.081, 1.537)

**Jin, M. et al. (2020) "Bayesian Approaches on Borrowing Historical Data for Vaccine Efficacy Trials". Statistics in Biopharmaceutical Research 12: 284-292*
Source: Table 1 in Response to CBER IR Dated 20 April 2023

The posterior mean of VE and its credible interval reported by the applicant were similar to alternative analyses conducted by the statistical reviewer using the data from study CYD14 (including all age groups). In these analyses, a Bayesian hierarchical model was fit to the three age groups (2 – 5, 6 – 8, and 9 – 16 years), along with a random age by treatment effect. The random interaction effect invokes borrowing of statistical information across age groups to the extent that

results are similar across groups. Different non-informative priors, including normal distribution and Dirichlet process mixture (DPM), were used for the interaction term. This resulted in increased precision for the estimate of VE, as well as shrinkage of the VE estimates of all age groups toward an overall mean (Table 27).

Table 27: Bayesian hierarchical models to estimate VE against symptomatic VCD across age groups in CYD14

Age group	VE estimates (95% confidence interval) from Table 19 and Table 20	Posterior median (95% credible interval) of VE Hierarchical Normal*	Posterior median (95% credible interval) of VE Hierarchical DPM** model
2 – 5	71.6% (10.7%, 91.7%)	75.1% (47.6%, 88.1%)	73.8% (37.1%, 88.69%)
6 – 8	67.8% (-11.8%, 91.7%)	73.7% (40.3%, 87.6%)	70.5% (19.28%, 87.4%)
9 – 16	79.2% (47.2%, 92.7%)	76.6% (54.2%, 88.5%)	79.0% (55.5%, 90.9%)

*See Pennello and Rothman (2018) "Bayesian Subgroup Analysis with Hierarchical Models" in K. E. Peace et al. (eds.), *Biopharmaceutical Applied Statistics Symposium* Hyperparameters were chosen to be non-informative, and followed guidelines in the article.
**See Olhssen et al. (2007). "Flexible random-effects models using Bayesian semi-parametric models: Applications to institutional comparisons". *Statistics in Medicine,* 26: 2088-2112. Results were consistent across hyperparameter selections that followed guidelines in the article.
Source: Reviewer-created table

In summary, the Bayesian VE analyses conducted by the applicant and the statistical reviewer relied on less stringent and clinically justifiable assumptions and showed consistent VE results (~70%) in seropositive subjects 6-8 years of age. Even though these Bayesian analyses were based on subjects in the immunogenicity subset in a single study (CYD14), the pooled analysis based on subjects in the immunogenicity subset of CYD14 and CYD23 (noting that CYD15 did not recruit subjects <9 years of age) showed a consistent VE of 71.6% with 95% CI: 28.9%, 88.7% (Table 18). Furthermore, results from the MI approach and NS1 approached, despite the caveats noted by the statistical reviewer, showed consistent VE results, further supporting the conclusion of effectiveness of the vaccine against symptomatic VCD in seropositive subjects 6-8 years of age.

HVCD in Baseline Dengue Seropositive Subjects

In the SafAS Efficacy Studies Integrated/Pooled analysis set (defined in this context as subjects who received at least 1 injection of CYD dengue vaccine or placebo), there were 2848 subjects aged 6 to 8 years in the CYD dengue vaccine Group. Among these subjects, a total of 129 HVCD cases were observed over the Entire Study period, including 8 cases in baseline seronegative subjects and 7 cases in baseline seropositive subjects from the Immunogenicity Subset. In the Placebo Group, 1425 subjects aged 6 to 8 years were part of the SafAS Efficacy Studies Integrated/Pooled analysis set. Among these subjects, there were 89 HVCD cases over the Entire Study period, including 3 cases in baseline seronegative subjects and 10 cases in baseline seropositive subjects from the Immunogenicity Subset.

RR of HVCD due to any serotype during the Entire Study Period (Immunogenicity Subset)

In seropositive subjects aged 6 to 8 years (CYD14 + CYD23/57), the estimated relative risk (RR) of HVCD due to any serotype during the Entire Study Period (up to 6 years after the first injection) for CYD Vaccine versus Placebo was 0.378 with 95% CI (0.12, 1.10). See Table 28.

In seropositive subjects aged 9 to 16 years, HVCD cases were reported only in the Placebo Group with 4 cases in CYD14 and 2 cases in CYD15. No HVCD cases were reported during the CYD23/57 Active Phase. The estimated RR of HVCD due to any serotype during the Entire Study Period for CYD Vaccine versus Placebo was 0.286 with 95% CI (0.12, 0.66).

In the combined population of seropositive subjects aged 6 to 16 years (CYD14 + CYD15 + CYD23/57), estimated RR of HVCD due to any serotype during the Entire Study Period for CYD Vaccine versus Placebo was 0.31 with 95% CI (0.16, 0.59).

Table 28: Incidence of HVCD due to any serotype during the Entire Study Period - baseline dengue seropositive subjects aged 9 to 16 years, 6 – 8 years, and 6 – 16 years who received at least 1 dose - Immunogenicity Subset (CYD23/57, CYD14, and CYD15) - SafAS Efficacy Studies Pooled

Age Group and Study	CYD Vaccine Cases	CYD M	Annual incidence rate	95% CI	n occurrences	Placebo Cases	Placebo M	Annual incidence rate	95% C I	n occurrences	RR	95% CI
9-16 years All studies	10	1523	0.1	(0.1; 0.2)	10	17	740	0.4	(0.2; 0.6)	17	0.286	(0.12; 0. 66)
CYD14	6	479	0.2	(0.1; 0.5)	6	9	249	0.6	(0.3; 1.1)	9	0.347	(0.10; 1.09)
CYD15	4	992	<0.1	(0.0; 0.2)	4	8	472	0.3	(0.1; 0.6)	8	0.238	(0.05; 0.89)
CYD23/57	0	53	0.0	(0.0; 1.1)	0	0	19	0.0	(0.0; 2.9)	0	NC	(NC)
6 – 8 years All studies	7	226	0.5	(0.2, 1.0)	7	10	122	1.4	(0.7; 2.4)	10	0.378	(0 12, 1.10)
CYD14	6	168	0.6	(0.2, 1 3)	6	8	87	1.5	(0.7; 2.9)	8	0.388	(0.11, 1.28)
CYD23/57	1	58	0.3	(0.0, 1 5)	1	2	35	1.0	(0.1; 3.2)	2	0.302	(0.01, 5.80)
6-16 years All studies	17	1749	0.2	(0.1; 0.3)	17	27	862	0.5	(0.3; 0.8)	27	0.310	(0.16; 0.59)
CYD14	12	647	0.3	(0.2; 0.5)	12	17	336	0.8	(0.5; 1.3)	17	0.367	(0.16; 0.81)
CYD15	4	992	<0.1	(0.0; 0.2)	4	8	472	0.3	(0.1; 0.6)	8	0.238	(0.05; 0.89)
CYD23/57	1	110	0.2	(0.0; 0.8)	1	2	54	0.6	(0.1; 2.1)	2	0.245	(0.00; 4.71)

M: mean of number of subjects followed during the years included in the considered period
Cases: number of subjects with at least one HVCD case in the considered period
Annual incidence rate = Cases among M * 100 converted in annual rate n occurrences: number of HVCD cases
CYD dengue vaccine 5 ± 1 log10 CCID50 of serotypes 1, 2, 3 and 4
Source: Tables 5.1, 5.3 and 5.5 Summary of Clinical Safety

Risk of HVCD due to any serotype during the Entire Study Period (NS1 Sub-Cohort)

To increase precision in RR estimates in the baseline seropositive subjects who were 6 – 8 years old, the applicant imputed baseline serostatus, as mentioned in Section 6.2 NS1 Close Out Supplemental Analysis, along with the case-cohort sampling, for those in the sub-cohort who were not in the Immunogenicity Subset.

The estimated relative risk of dengue hospitalization due to any serotype occurring during the Entire Study Period (M0- M25 for MI approaches and PD3-M25 for NS1 approaches) in subjects aged 6 to 8 years classified as baseline seropositive is shown in Table 29, with Table 30 for 9 to 16 year old subjects as reference.

Table 29: Estimated risk of HVCD due to any serotype during the Entire Study Period - subjects aged 6 to 8 years, classified as seropositive, and who received at least 1 dose - NS1 Supplemental Analyses (CYD23/57 and CYD14) - SafAS Efficacy Studies Integrated/Pooled

--	CYD vaccine Group Cases n (N)	Placebo Group Cases n (N)	Risk of HVCD Hazard Ratio	95% Confidence Interval
All Studies 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 (Thr9) M13	36 (155)	44 (75)	0.404	(0.243, 0.670)
NS1 (Thr50) M13	23 (123)	30 (56)	0.356	(0.193, 0.657)
CYD14 MI $PRNT_{50}$ M0	25.8 (99.2)	38.5 (51.8)	0.334	(0.168, 0.668)
MI $PRNT_{90}$ M0	13.7 (82.5)	34.5 (45.7)	0.209	(0.096, 0.454)
NS1 (Thr9) M13	19 (93)	27 (44)	0.338	(0.174, 0.655)
NS1 (Thr50) M13	13 (76)	19 (34)	0.309	(0.141, 0.677)
CYD23/57 MI $PRNT_{50}$ M0	20.2 (65)	22.1 (32.7)	0.459	(0.181, 1.166)
MI $PRNT_{90}$ M0	6.2 (44.9)	16.6 (24.7)	0.212	(0.060, 0.749)
NS1 (Thr9) M13	17 (62)	17 (31)	0.516	(0.237, 1.125)
NS1 (Thr50) M13	10 (47)	11 (22)	0.451	(0.172, 1.179)

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: Table 5.4 summary of clinical safety

Table 30: Estimated risk of HVCD due to any serotype during the Entire Study Period - subjects aged 9 to 16 years, classified as seropositive, and who received at least 1 dose - NS1 Supplemental Analyses (CYD23/57, CYD14, and CYD15) - SafAS Efficacy Studies Pooled

--	CYD vaccine Group Cases n (N)	Placebo Group Cases n (N)	Risk of HVCD Hazard Ratio	95% Confidence Interval
CYD14 + CYD15 + CYD23/57 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 (Thr9) M13	51 (1460)	113 (687)	0.213	(0.151, 0.300)
NS1 (Thr50) M13	31 (1302)	70 (587)	0.201	(0.131, 0.311)

CYD14 MI $PRNT_{50}$ M0	27.3 (293.9)	54.1 (151.8)	0.262	(0.148, 0.463)
MI $PRNT_{90}$ M0	15.7 (270.3)	52.1 (144.6)	0.161	(0.076, 0.344)
NS1 (Thr9) M13	26 (293)	44 (137)	0.278	(0.166, 0.468)
NS1 (Thr50) M13	16 (262)	26 (114)	0.272	(0.142, 0.524)
CYD15 MI $PRNT_{50}$ M0	19.2 (1140.3)	62.2 (544.2)	0.143	(0.071, 0.289)
MI $PRNT_{90}$ M0	11.7 (1076.3)	59.2 (531.8)	0.096	(0.048, 0.191)
NS1 (Thr9) M13	15 (1107)	50 (518)	0.141	(0.078, 0.253)
NS1 (Thr50) M13	8 (988)	32 (450)	0.115	(0.052, 0.251)
CYD23/57 MI $PRNT_{50}$ M0	9.7 (61.7)	20.8 (33)	0.253	(0.097, 0.658)
MI PRNT90 M0	6 (50.2)	17.2 (26.5)	0.184	(0.053, 0.640)
NS1 (Thr9) M13	10 (60)	19 (32)	0.286	(0.122, 0.670)
NS1 (Thr50) M13	7 (52)	12 (23)	0.262	(0.094, 0.730)

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: Table 5.2 summary of clinical safety

Sensitivity Analysis (Analogous to that for Symptomatic VCD)

The same sensitivity analysis that was conducted for the endpoint of VE against symptomatic VCD was also done for the HVCD endpoint.

Results for the 6 – 8 age group are reported for studies CYD14+CYD23/57. However, results for the 9 – 16 years age group are reported for CYD14+CYD15+CYD23/57, as the applicant did not report PRNT and MI results for the combined studies CYD14+CYD23/57.

There is a similar pattern for HVCD as noted for symptomatic VCD, but much less pronounced (see Table 31). That is, for the 6 – 8 age group, the MI model tended to slightly misclassify vaccine seropositive cases as seronegative (reducing the number of cases in the seropositive category for the CYD group) but tended to misclassify seronegative placebo cases as seropositive (slightly increasing the number of cases in the seropositive category for placebo). This pattern did not occur with the 9 – 16 age group (Table 32).

Table 31: HR for HVCD - Immunogenicity Subset 6-8 years (Seropositive) CYD14+CYD23/57

--	**PRNT50 criterion**	**MI model[#]**
HR (95% CI)	0.378 (0.12, 1.10)	0.223 (0.057, 0.877)
CYD Vaccine Cases	7	6.2
Placebo Cases	10	10.8

[#]The MI model results include only ImmSubset subjects who were in the subcohort. But they include all cases.
Source: Reviewer-created table using information from Response to CBER IR Dated 14 Oct 2022

Table 32: HR for HVCD - Immunogenicity Subset 9-16 years (Seropositive) CYD14+CYD15+CYD23/57

--	**PRNT50 criterion**	**MI model[#]**
HR (95% CI)	0.286 (0.12, 0.66)	0.314 (0.129, 0.764)
CYD Vaccine Cases	10	10.5
Placebo Cases	17	15.7

[#]The MI model results include only ImmSubset subjects who were in the subcohort. But they include all cases.
Source: Reviewer-created table using information from Response to CBER IR Dated 14 Oct 2022

Similarly to Symptomatic VCD endpoint, the applicant fit a Bayesian model with a power prior where information from other age groups (2-5 years and 9-16 years) was used to construct the power prior distribution. The resulting posterior mean of the HR for the 6 – 8 age group was 0.398 with a 95% credible interval of (0.173, 0.892) as shown in Table 26.

Risk of SVCD in Baseline Dengue Seropositive Subjects

In the SafAS Efficacy Studies Integrated/Pooled analysis set, there were 2848 subjects aged 6 to 8 years in the CYD dengue vaccine Group. Among these subjects, a total of 20 SVCD cases were observed over the Entire Study period, including 2 cases in baseline seropositive subjects from the Immunogenicity Subset.

In the Placebo Group, 1425 subjects aged 6 to 8 years were part of the SafAS Efficacy Studies Integrated/Pooled analysis set. Among these subjects, there were 16 SVCD cases over the Entire Study period, including 3 cases in baseline seropositive subjects from the Immunogenicity Subset.

In baseline seropositive subjects aged 9 to 16 years, there was one SVCD case in the CYD vaccine group and 3 in the Placebo Group over the entire study period.

In the Immunogenicity Subset, in seropositive subjects aged 6 to 8 years (CYD14+CYD23/57), the RR of SVCD due to any serotype during the Entire Study Period for the CYD vaccine group over the Placebo group was 0.360 with 95% CI (0.03, 3.14). The RR estimate of SVCD in older seropositive children aged 9 to 16 years was 0.162, with 95% CI: (0.0, 2.02), and in the pooled age group of 6 to 16 years was 0.246 (0.04, 1.15). See Table 33.

Table 33: Incidence of SVCD due to any serotype during the Entire Study Period - baseline dengue seropositive subjects aged 6 to 8 years, 9 to 16 years, and 6 to 16 years who received at least 1 dose - Immunogenicity Subset (CYD23/57, CYD14, and CYD15) - SafAS Efficacy Studies Integrated/Pooled

--	CYD Vaccine Cases	M	Annual incidence rate	(95% CI)	n occurrences	Placebo Cases	M	Annual incidence rate	(95% CI)	n occurrences	RR	95% CI
9-16 years All studies	1	1523	<0.1	(0.0; 0.1)	1	3	740	<0 1	(0.0; 0.2)	3	0.162	(0.00; 2.02)
CYD14	0	479	0.0	(0.0; 0.1)	0	1	249	<0 1	(0.0; 0.4)	1	0.000	(0.00; 20.27)
CYD15	1	992	<0.1	(0.0; 0.1)	1	2	472	<0 1	(0.0; 0.3)	2	0.238	(0.00; 4.57)
CYD23/57	0	53	0.0	(0.0; 1.1)	0	0	19	0.0	(0.0; 2.9)	0	NC	(NC)
6 – 8 years All studies	2	226	0.1	(0.0, 0.5)	2	3	122	0.4	(0.1; 1.2)	3	0.360	(0.03; 3.14)
CYD14	2	168	0.2	(0.0; 0.7)	2	3	87	0.6	(0.1; 1.6)	3	0.345	(0.03; 3.01)
CYD23/57	0	58	0.0	(0.0; 1.0)	0	0	35	0.0	(0.0; 1.7)	0	NC	(NC)
6-16 years All studies	3	1749	<0.1	(0.0; 0.1)	3	6	862	0 1	(0.0; 0.3)	6	0.246	(0.04; 1.15)
CYD14	2	647	<0.1	(0.0; 0.2)	2	4	336	0 2	(0.1; 0.5)	4	0.260	(0.02; 1.81)
CYD15	1	992	<0.1	(0.0; 0.1)	1	2	472	<0 1	(0.0; 0.3)	2	0.238	(0.00; 4.57)
CYD23/57	0	110	0.0	(0.0; 0.5)	0	0	54	0.0	(0.0; 1.1)	0	NC	(NC)

M: mean of number of subjects followed during the years included in the considered period
Cases: number of subjects with at least one SVCD case in the considered period
Annual incidence rate = Cases among M * 100 converted in annual rate n occurrences: number of SVCD cases
CYD dengue vaccine 5 ± 1 log10 CCID50 of serotypes 1, 2, 3 and 4
Source: Tables 5.25, 5.27, and 5.29 Summary of Clinical Safety

Similarity to the Symptomatic VCD and HVCD endpoints, the applicant fit a Bayesian model with a power prior where information from other age groups (2-5 years and 9-16 years) was used to construct the power prior distribution. The resulting posterior mean of the HR for the 6 – 8 age group was 0.367 with a 95% credible interval of (0.081, 1.537) as shown in Table 26.

Risk of SVCD due to any serotype during the Entire Study Period (NS1 Sub-Cohort)

To increase precision in relative risk estimates in the baseline seropositive subjects who were 6 – 8 years old, the applicant used the methods of imputation of serostatus, as mentioned in Section 6.2 NS1 Close Out Supplemental Analysis, along with the case-cohort sampling, to impute serostatus for those in the sub-cohort who were not in the Immunogenicity Subset.

The risk of severe dengue due to any serotype occurring during the Entire Study Period in subjects aged 6 to 8 years classified as baseline seropositive is shown in Table 34 with Table 35 for comparison in 9 to 16 years old subjects.

Table 34: Estimated risk of SVCD due to any serotype during the Entire Study Period - subjects aged 6 to 8 years, classified as seropositive, and who received at least 1 dose - NS1 Supplemental Analyses (CYD23/57 and CYD14) - SafAS Efficacy Studies Integrated/Pooled

--	CYD vaccine Group Cases n (N)	Placebo Group Cases n (N)	Risk of SVCD Hazard Ratio	95% Confidence Interval
All Studies 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 (Thr9) M13	9 (155)	11 (75)	0.400	(0.162, 0.990)
NS1 (Thr50) M13	4 (123)	8 (56)	0.231	(0.068, 0.783)
CYD14 MI $PRNT_{50}$ M0	7.5 (99.2)	11.5 (51.8)	0.321	(0.090, 1.142)
MI $PRNT_{90}$ M0	5 (82.5)	11.1 (45.7)	0.243	(0.073, 0.809)
NS1 (Thr9) M13	7 (93)	9 (44)	0.368	(0.133, 1.019)
NS1 (Thr50) M13	4 (76)	7 (34)	0.256	(0.073, 0.894)
CYD23/57 MI $PRNT_{50}$ M0	1.3 (65)	1.7 (32.7)	N/A	N/A
MI $PRNT_{90}$ M0	0.3 (44.9)	1.7 (24.7)	N/A	N/A
NS1 (Thr9) M13	2 (62)	2 (31)	0.506	(0.072, 3.581)
NS1 (Thr50) M13	0 (47)	1 (22)	N/A	N/A

Source: Table 5.28 Summary of Clinical Safety

Table 35: Estimated risk of SVCD due to any serotype during the Entire Study Period - subjects aged 9 to 16 years, classified as seropositive, and who received at least 1 dose - NS1 Supplemental Analyses (CYD23/57, CYD14, and CYD15) - SafAS Efficacy Studies Integrated/Pooled

--	CYD vaccine Group Cases n (N)	Placebo Group Cases n (N)	Risk of HVCD Hazard Ratio	95% Confidence Interval
CYD14 + CYD15 + CYD23/57 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 (Thr9) M13	10 (1460)	28 (687)	0.168	(0.082, 0.348)
NS1 (Thr50) M13	5 (1302)	17 (587)	0.134	(0.049, 0.364)
CYD14 MI $PRNT_{50}$ M0	5.6 (293.9)	17.6 (151.8)	0.161	(0.046, 0.561)
MI $PRNT_{90}$ M0	2.8 (270.3)	17.6 (144.6)	0.086	(0.022, 0.341)
NS1 (Thr9) M13	4 (293)	15 (137)	0.126	(0.041, 0.386)
NS1 (Thr50) M13	2 (262)	10 (114)	0.088	(0.019, 0.408)
CYD15 MI $PRNT_{50}$ M0	3.6 (1140.3)	14.7 (544.2)	0.107	(0.024, 0.469)
MI $PRNT_{90}$ M0	2.1 (1076.3)	13.4 (531.8)	0.075	(0.014, 0.408)
NS1 (Thr9) M13	4 (1107)	11 (518)	0.170	(0.054, 0.536)
NS1 (Thr50) M13	1 (988)	5 (450)	0.092	(0.011, 0.787)

--	CYD vaccine Group Cases n (N)	Placebo Group Cases n (N)	Risk of HVCD Hazard Ratio	95% Confidence Interval
CYD23/57 MI $PRNT_{50}$ M0	2.2 (61.7)	1.9 (33)	0.614	(0.078, 4.814)
MI PRNT90 M0	1.4 (50.2)	1.6 (26.5)	N/A	N/A
NS1 (Thr9) M13	2 (60)	2 (32)	0.533	(0.075, 3.791)
NS1 (Thr50) M13	2 (52)	2 (23)	0.442	(0.062, 3.133)

Source: Table 5.26 Summary of Clinical Safety

Sensitivity Analysis (Analogous to that for Symptomatic VCD)

The same sensitivity analysis that was conducted for the endpoint of VE against symptomatic VCD and for HVCD was also done for the SVCD endpoint.

Results for the 6 – 8 age group are reported for studies CYD14+CYD23/57. However, results for the 9 – 16 year age group are reported for CYD14+CYD15+CYD23/57, as the applicant did not report PRNT and MI results for the combined studies CYD14 + CYD23/57. See Table 36 and Table 37.

For the 6 – 8 age group, the MI model tended to misclassify seropositive cases as seronegative on average, for both vaccine and placebo groups). The applicant was not able to obtain a reliable RR estimate using the MI model due to the low number of cases per group. However, the average number of cases appears in the tables.

Table 36: HR for SVCD - Immunogenicity Subset 6-8 years (Seropositive) CYD14+CYD23/57

--	PRNT50 criterion	MI model
HR (95% CI)	0.360 (0.03, 3.14)	Not calculated
CYD Vaccine Cases	2	0.8
Placebo Cases	3	2.2

Source: Reviewer-created table using information from Response to CBER IR Dated 14 Oct 2022

Table 37: HR for SVCD - Immunogenicity Subset 9-16 years (Seropositive) CYD14+CYD15+CYD23/57

--	PRNT50 criterion	MI model
HR (95% CI)	0.162 (0.0, 2.02)	Not calculated
CYD Vaccine Cases	1	1.6
Placebo Cases	3	2.3

Source: Reviewer-created table using information from Response to CBER IR Dated 14 Oct 2022

7.1.5 Other Endpoints

NA

7.1.6 Subpopulations

Results are presented for the 6 to 8 years age group and 9 to 16 years age group.

7.1.7 Additional Efficacy Issues/Analyses

CBER considered the possibility of using the NS1 titer at M13 threshold as a surrogate for baseline serostatus in order to estimate the relative risk of symptomatic, hospitalized and severe VCD after M0. One complication with such an approach is that subjects who contracted dengue between M0 and M13, but were seronegative at M0, would in theory report a positive NS1 result at M13. Therefore, CBER requested that the applicant perform a tipping point analysis that assessed to what extent these potential misclassifications could have on VE and RR estimated with all missing PRNT50 baseline serostatuses imputed with the NS1 threshold serostatus up to a worst-case scenario where all placebo subjects with VCD between M0 and M13 were considered seronegative at baseline but vaccine subjects with VCD between M0 and M13 remained seropositive.

For the analysis, the applicant used all 6 – 8 years old subjects in CYD14 with either PRNT50 available or NS1 at M13 (if PRNT50 missing). This set contained 730 subjects: 457 Vaccine subjects and 273 Placebo subjects. In addition, 42 of the 457 Vaccine subjects had VCD in M0-M13, and 44 of the 273 Placebo subjects had VCD in M0-M13. See Table 38.

Of the 730 total subjects, 480 (289 Vaccine, 191 Placebo) were seropositive using either PRNT50 or NS1 at M13. Of those seropositive by this method, 40 Vaccine subjects had VCD in M0-M13 and 43 Placebo subjects had VCD in M0-M13. Nine Vaccine and 11 Placebo subjects had HVCD in M0-M13; and one subject in each group had SVCD.

Table 38: Numbers of 6 – 8 year old Subjects in Tipping Point Analysis by Treatment Group (CYD14)

Number of Subjects	**CYD Vaccine (n)**	**Placebo (n)**
Number of 6 – 8 year old subjects in CYD14	457	273
Number with VCD in M0-M13	42	44
Number Seropositive by PRNT50 or NS1 M13>9	289	191
Number seropositive with VCD in M0-M13	40*	43**
Number seropositive with HVCD in M0-M13	9	11
Number seropositive with SVCD in M0-M13	1	1

Number of Subjects	CYD Vaccine (n)	Placebo (n)
Number seropositive by PRNT50 or NS1 M13 and in the sub-cohort	97	50
Number seropositive with VCD cases (including M0-M13 cases)	54	58
Number seropositive with HVCD cases (including M0-M13 cases)	50	56
Number seropositive with SVCD cases (including M0-M13 cases)	11	12

*One Vaccine VCD in M0-M13 was negative by PRNT50, another was negative by NS1 at M13 (with missing PRNT50)
**One placebo VCD in M0-M13 was negative by NS1 at M13 (with missing PRNT50)
Source: Reviewer-created table

For symptomatic VCD, the tipping point analysis was inconclusive in that when 14/58 (about 24%) placebo cases in M0-M13 were moved out of the seropositive category to the seronegative category, toward the "worst case", the resulting lower confidence limit (LCL) on VE dropped below 0%.

For hospitalized VCD, the applicant used only HVCD cases during M0-M13 for the tipping point analysis. There were 9 such cases in the Vaccine group, and 11 in the Placebo group. Because the HVCD endpoint started from M0, all HVCD in M0-M13 are included within the total 50 and 56 HVCD case counts for the analysis (see Table 39). Then, they moved each placebo M0-M13 VCD case out of the seropositive category to the seronegative category. Table 39 below shows that a worst-case HR estimate of hospitalization was 0.561 with upper 95% confidence limit of 0.898, which is less than 1.0, indicating no increased risk of HVCD in the worst-case scenario.

Table 39: Tipping point for Risk of dengue hospitalization occurring after M0 in subjects aged 6-8 years - Subjects classified as seropositive by Mixed PRNT50 and NS1 M13 - CYD14+CYD23/57

Cases Vaccine Group n (N)	Cases Placebo Group n (N)	Cases All Subjects n (N)	CYD Group D0-M13 VCD Seroneg/Seropos cases	Placebo Group D0-M13 VCD Seroneg/Seropos cases	Comparison	HVCD Hazard Ratio	95% Confidence Interval
50 (161)	56 (82)	106 (243)	0 / 9	0 / 11	CYD Dengue Vaccine vs. Placebo	0.452	(0.288, 0.711)
50 (161)	45 (80)	95 (241)	0 / 9	11 / 0	CYD Dengue Vaccine vs. Placebo	0 561	(0.350, 0.898)

n: number of subjects fulfilling the item listed
N: total number of subjects selected in sub-cohort
Study group classified as randomized (Subjects classified according to the injection assigned at randomization) Mixed PRNT50 and NS1 M13 is equal to PRNT50 baseline status when available and completed with NS1 M13 status if missing
Source: Table 2 in Response to CBER Information Request Dated 14 Oct 2022

For severe VCD, the applicant used only severe VCD (SVCD) cases in M0-M13 for the tipping point analysis. There was 1 such case each in the Vaccine and Placebo groups. Because the SVCD endpoint started from M0, all SVCD in M0-M13 are included within the total 11 and 12 SVCD case counts for Vaccine and Placebo, respectively (see Table

40), with a HR estimate of 0.472 (95% CI: 0.203;1.098). There was one placebo severe case between M0-M13 classified as seropositive, and when switched to seronegative, the estimated HR increased to 0.515 (95% CI: 0.218;1.218).

Table 40: Tipping point for Risk of severe dengue (IDMC) occurring after M0 in subjects aged 6-8 years - Subjects classified as seropositive by Mixed PRNT50 and NS1 M13 - CYD14+CYD23/57

Cases Vaccine Group n (N)	Cases Placebo Group n (N)	Cases All Subjects n (N)	CYD Group D0-M13 VCD Seroneg/Seropos cases	Placebo Group D0-M13 VCD Seroneg/Seropos cases	Comparison	SVCD Hazard Ratio	95% Confidence Interval
11 (161)	12 (82)	23 (243)	0 / 1	0 / 1	CYD Dengue Vaccine vs. Placebo	0.472	(0.203, 1.098)
11 (161)	11 (82)	22 (243)	0 / 1	1 / 0	CYD Dengue Vaccine vs. Placebo	0 515	(0.218, 1.218)

n: number of subjects fulfilling the item listed
N: total number of subjects selected in sub-cohort
Study group classified as randomized (Subjects classified according to the injection assigned at randomization) Mixed PRNT50 and NS1 M13 is equal to PRNT50 baseline status when available and completed with NS1 M13 status if missing
Source: Table 5 in Response to CBER Information Request Dated 14 Oct 2022

Thus, for HVCD, the tipping point analysis showed that the results reported by the applicant that used the NS1 titer threshold of 9 at M13 for imputing baseline serostatus could lend support to the reported MI results. For symptomatic VCD, the tipping point analysis did not yield conclusive support. For severe VCD, the number of severe VCD cases was too small to draw conclusion, yet the point estimates of RR for SVCD are consistently well below 1, even in the worst case scenario.

7.1.8 Efficacy Conclusions

Table 41 summarizes the major clinical efficacy analyses conducted by the applicant for the 6 – 8 years old seropositive subjects.

Table 41: Estimated risk against symptomatic VCD (during active phase), HVCD (during entire study period) and SVCD (during entire study period) due to any serotype in subjects aged 6 to 8 years classified as seropositive (observed/imputed)

Analysis	VCD VE(%)	95% CI	HVCD Hazard Ratio	95% CI	SVCD Hazard Ratio	95% CI
Immunogenicity subset	67.8	(-11.8,91.7)	0.388	(0.11, 1.28)	0.345	(0.03, 3.01)
MI $PRNT_{50}$ M0	67.3	(39.9, 82.2)	0.262	(0.148, 0.463)	0.321	(0.090, 1.142)
NS1 (Thr9) M13	55.8	(1.8, 80.1)	0.278	(0.166, 0.468)	0.368	(0.133, 1.019)
Conditional binomial model with power beta prior	72.6	(40.9, 88.1)	0.398	(0.173, 0.892)	0.367	(0.081, 1.537)

Source: Modified from Table 1 in Response to CBER Information Request Dated 20 Apr 2023

As discussed, the collective evidence from various VE analyses showed consistent VE results (~70%) in seropositive subjects 6-8 years of age, supporting the conclusion of effectiveness of the vaccine against symptomatic VCD in seropositive subjects 6-8 years of age. In addition, the HVCD and SVCD analyses, including the tipping analysis, did not reveal evidence of increased risk among seropositive subjects 6-8 years of age.

8. INTEGRATED OVERVIEW OF IMMUNOGENICITY

The main objective of the Integrated Immunogenicity Analysis was to provide an overview of the humoral immune response against each and any dengue serotype induced by the CYD dengue vaccine, by age and region, in baseline dengue seropositive subjects, with a focus on the response 28 days post-Dose 3 (PD3).

A secondary objective was to provide an overview of the persistence of the humoral immune response to the CYD dengue vaccine at baseline, 28 days PD3, and yearly PD3 time points, by age group and region, in baseline seropositive subjects, using data collected from the pivotal and supportive studies.

8.1 Immunogenicity Assessment Methods

The $PRNT_{50}$ assay was used to measure the humoral immune response induced by the CYD dengue vaccine in all studies. The main parameters assessed were the geometric mean titers (GMTs), and geometric mean of titer ratios (GMTRs). The Full Analysis Set (FAS), which included all subjects who received at least one injection, was used to present immunogenicity results.

8.2 Immunogenicity Database

8.2.1 Studies/Clinical Trials Used to Evaluate Immunogenicity

Six studies included subjects aged 6 to 8 years of age and were considered for an integrated analysis of immunogenicity (CYD14, CYD22, CYD23, CYD24, CYD28, and CYD32). GMTs are presented pre-dose 1 and post-dose 3. Persistence data up to 5 years after the third injection are also presented, when available.

8.3 Immunogenicity Results

GMTs at baseline and 28 days after the third injection of the CYD dengue vaccine are presented in baseline seropositive subjects aged 6 to 8 years by endemic region in Table 42.

Table 42: Geometric means of Dengue PRNT50 antibody (1/dil) pre-Dose 1 and PD3 for each serotype, in seropositive subjects aged 6 to 8 years – FAS

Region	Study	N	Serotype 1 Pre-dose 1 GM (M) (95% CI)	Serotype 1 Post-dose 3 GM (M) (95% CI)	N	Serotype 2 Pre-dose 1 GM (M) (95% CI)	Serotype 2 Post-dose 3 GM (M) (95% CI)	N	Serotype 3 Pre-dose 1 GM (M) (95% CI)	Serotype 3 Post-dose 3 GM (M) (95% CI)	N	Serotype 4 Pre-dose 1 GM (M) (95% CI)	Serotype 4 Post-dose 3 GM (M) (95% CI)
Endemic AP	CYD14	168	80.8 (167) (57.3; 114)	203 (166) (154; 268)	168	118 (168) (86.0; 161)	369 (166) (298; 457)	168	105 (168) (75.5; 145)	316 (166) (244; 411)	168	48.4 (168) (37.2; 63.0)	175 (166) (145; 211)
	CYD22	17	47.3 (17) (13.6; 164)	133 (15) (51.3; 343)	17	41.8 (17) (16.2; 108)	147 (15) (74.0; 292)	17	44.2 (17) (20.5; 95.3)	135 (15) (76.8; 237)	17	16.0 (17) (8.32; 30.9)	134 (15) (95.0; 190)
Endemic AP	CYD23	66	66.5 (66) (39.4; 112)	213 (63) (138; 329)	66	118 (66) (69.0; 202)	548 (63) (355; 844)	66	49.5 (66) (34.8; 70.5)	462 (63) (328; 651)	66	53.8 (66) (35.2; 82.2)	195 (63) (141; 269)

Region	Study	N	Serotype 1 Pre-dose 1 GM (M) (95% CI)	Serotype 1 Post-dose 3 GM (M) (95% CI)	N	Serotype 2 Pre-dose 1 GM (M) (95% CI)	Serotype 2 Post-dose 3 GM (M) (95% CI)	N	Serotype 3 Pre-dose 1 GM (M) (95% CI)	Serotype 3 Post-dose 3 GM (M) (95% CI)	N	Serotype 4 Pre-dose 1 GM (M) (95% CI)	Serotype 4 Post-dose 3 GM (M) (95% CI)
Endemic AP	**CYD28**	8	6.75 (8) (4.15; 11.0)	101 (8) (44.0; 231)	8	8.97 (8) (4.39; 18.4)	89.0 (8) (44.0; 180)	8	16.5 (8) (4.62; 59.0)	194 (8) (59.6; 629)	8	7.91 (8) (2.67; 23.4)	111 (8) (58.7; 208)
Endemic AP	**CYD32**	22	134 (22) (46.6; 385)	527 (22) (219; 1268)	22	93.6 (22) (32.0; 274)	585 (22) (330; 1038)	22	83.6 (22) (42.1; 166)	442 (22) (234; 835)	22	21.5 (22) (11.2; 41.3)	184 (22) (109; 309)
Endemic LatAm	**CYD24**	11	155 (11) (42.7; 560)	716 (11) (394; 1301)	11	92.8 (11) (36.4; 236)	250 (11) (184; 341)	11	139 (11) (40.4; 480)	530 (11) (266; 1058)	11	14.2 (11) (6.23; 32.4)	159 (11) (113; 224)

M: number of subjects with available Ab titer for the relevant endpoint
Source: Table 1.10 in Summary of Clinical Efficacy

In seropositive subjects aged 6 to 8 years, an increase in GMTs was observed for each of the four serotypes after 3 doses of the CYD dengue vaccine across the reported trials, with relatively higher values for serotypes 1, 2, and 3 and lower values for serotype 4. Of note, the pre- Dose 1 GMTs for serotype 4 were lower than other serotypes as well. Neutralizing Ab levels in the Control Group, overall, showed no increase in GMTs after any injection of the placebo, across the reported trials, in all age groups (not shown in memo).

In comparison to other age groups, pre-Dose 1 GMTs were higher in older subjects than in younger subjects and higher in high endemic settings compared to low endemic settings. Overall, a trend towards higher PD3 GMT levels was observed in subjects with higher baseline titers regardless of age group. As such, a trend towards increasing PD3 GMTs with increasing age and higher endemicity was observed.

GMTRs based on PD3 titers over baseline titers in seropositive subjects aged 6 to 8 years are presented in Table 43.

Table 43: Geometric mean ratios of PD3 to pre-Dose 1 Dengue PRNT50 antibody (1/dil) for each serotype, in seropositive subjects aged 6 to 8 years in the CYD vaccine group- FAS

Study	N	Serotype 1 GMTRs (M) (95% CI)	N	Serotype 2 GMTRs (M) (95% CI)	N	Serotype 3 GMTRs (M) (95% CI)	N	Serotype 4 GMTRs (M) (95% CI)
CYD14 Endemic AP	168	2.10 (165) (1.73; 2.56)	168	2.75 (166) (2.21; 3.42)	168	2.73 (166) (2.22; 3.34)	168	3.02 (166) (2.43; 3.75)
CYD22 Endemic AP	17	2.03 (15) (1.04; 3.97)	17	2.81 (15) (1.65; 4.78)	17	2.58 (15) (1.42; 4.71)	17	6.20 (15) (2.97; 12.9)
CYD23 Endemic AP	66	2.63 (63) (1.76; 3.95)	66	4.05 (63) (2.72; 6.03)	66	8.47 (63) (5.92; 12.1)	66	3.27 (63) (2.33; 4.57)
CYD28 Endemic AP	8	8.88 (8) (4.25; 18.5)	8	6.43 (8) (3.76; 11.0)	8	9.05 (8) (3.78; 21.7)	8	7.62 (8) (3.24; 17.9)
CYD32 Endemic AP	22	3.47 (22) (2.24; 5.38)	22	5.01 (22) (2.54; 9.87)	22	4.96 (22) (3.23; 7.62)	22	6.42 (22) (3.53; 11.7)
CYD24 Endemic LatAm	11	4.35 (11) (1.84; 10.3)	11	2.53 (11) (1.22; 5.25)	11	3.57 (11) (1.66; 7.70)	11	8.17 (11) (4.81; 13.9)

N: number of subjects with available Ab titer for the relevant endpoint
Source: Table 1.13 in Summary of Clinical Efficacy

GMTRs of PD3/baseline for each serotype in subjects 6 to 8 years ranged from 2.03 for serotype 1 in CYD22 to 9.05 for serotype 3 in CYD28.

Overall, a trend towards higher GMTRs of PD3/baseline was observed with decreasing age, with the highest being in the youngest age group of 2 to 5 years (not shown in memo). A similar trend was observed in lower endemic settings compared to higher endemic settings.

9. INTEGRATED OVERVIEW OF SAFETY

This section focuses on studies that assessed integrated/pooled safety in the 6 – 8 years age group.

9.1 Safety Assessment Methods

Clinical safety was assessed in all studies, in terms of immediate reactions, solicited injection site and systemic reactions, unsolicited non-serious AEs, and SAEs. Clinical safety assessment with respect to long-term HVCD or SVCD was discussed in Section 7.1.4 Analysis of Primary Endpoints.

The safety after any of the 3 doses in the CYD dengue vaccine Group (including subjects who have received at least 1 injection of the CYD dengue vaccine) was compared to the Placebo Group (including subjects who received at least one injection of placebo and no CYD dengue vaccine or comparator vaccine), and to the Control Group (including subjects who received at least 1 injection of either placebo or comparator vaccine and no CYD dengue vaccine).

The SafAS was defined as subjects who received at least 1 injection of CYD dengue vaccine, placebo or comparator vaccine. Subjects were analyzed according to the product received; subjects who received an incorrect investigational product were included only in the subset for analyses related to the corresponding individual dose.

9.2 Safety Database

9.2.1 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 (D0/M6/M12) in subjects ≥ 6 years, referred to as the "Main Studies", were part of the integrated/pooled safety analyses. For the analysis of the safety profile of the CYD dengue vaccine up to 6 months after the third injection, pooled data of the 6 Main Studies (CYD14, CYD22, CYD23, CYD24, CYD28, and CYD32) in the 6 to 8 years age group were analyzed.

9.2.2 Overall Exposure, Demographics of Pooled Safety Populations

A total of 3233 individuals aged 6 to 8 years received at least one dose of the CYD dengue vaccine with the 3-dose schedule and were included in the safety analyses (after

any of the 3 doses), in which the occurrence of SAEs and adverse events of special interest (AESIs) was assessed. Among them, 294 subjects were known to be baseline dengue seropositive. In addition, 768 subjects aged 6 to 8 years, of whom 294 were seropositive, provided data to assess the reactogenicity of the final formulation of the CYD dengue vaccine according to the 3-dose schedule. See Table 44.

Table 44: Number of subjects considered for the assessment of safety

Safety Assessment	6 – 8 years CYD vaccine	6 – 8 years Placebo	6 – 8 years Control	9 – 16 years CYD vaccine	9 – 16 years Placebo	9 – 16 years Control	6 – 16 years CYD vaccine	6 - 16 years Placebo	6 – 16 years Control
Overall safety in seropositive subjects	294	110	152	2405	817	1023	2699	927	1175
Overall safety in subjects regardless of the serostatus	3233	1505	1597	19715	9163	9492	22948	10668	11089
Reactogenicity in seropositive subjects	294	110	152	2405	817	1023	2699	927	1175
Reactogenicity in all subjects regardless of the serostatus	768	278	370	3666	1152	1481	4434	1430	1851

Source: Table 2 in Clinical Overview

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

All studies in the ISS for children aged 6 – 8 years were randomized, controlled studies conducted in healthy subjects. Although the procedures for the collection of the safety data evolved throughout the clinical development program, the time points and main endpoints were similar.

Different comparator vaccines, mainly the rabies vaccine (in CYD23), the pneumococcal vaccine (in CYD24), and the hepatitis A vaccine (in CYD28), were used in subjects aged 6 to 8 years. These subjects constituted the "control" group in the tables below. The sample size for comparator vaccines was limited (around 25 subjects for each of the comparators).

9.4 Safety Results

A safety overview is presented in Table 45 for all children aged 6 to 8 years regardless of the serostatus after any of 3 doses of CYD dengue vaccine dose or Placebo or Control, as well as in baseline dengue seropositive children aged 6 to 8 years after any of 3 doses of CYD dengue vaccine dose.

Table 45: Safety overview in children aged 6 to 8 years regardless of the serostatus after any of 3 doses of CYD dengue vaccine dose or Placebo or Control, and in baseline dengue seropositive children aged 6 to 8 years after any of 3 doses of CYD dengue vaccine dose - SafAS Main Studies Pooled

REACTOGENICITY SUBSET **Subjects experiencing at least one:**	**CYD (all) n/M**	**%**	**95% CI**	**Placebo (all) n/M**	**%**	**95% CI**	**Contol (all) n/M**	**%**	**95% CI**	**CYD Seropositive n/M**	**%**	**95% CI**
Immediate unsolicited AE	0/768	0.0	(0.0; 0.5)	0/278	0.0	(0.0; 1 3)	0/370	0.0	(0.0; 1.0)	0/294	0.0	(0.0; 1.2)
Solicited reaction	586/766	76.5	(73.3; 79.5)	196/278	70.5	(64.8; 75.8)	261/370	70.5	(65.6; 75.1)	197/293	67.2	(61.5; 72.6)
Grade 3 solicited reaction	45/766	5 9	(4.3; 7.8)	25/278	9.0	(5.9; 13.0)	31/370	8.4	(5.8; 11.7)	20/293	6.8	(4.2; 10.3)
Solicited injection site reaction	430/766	56.1	(52.5; 59.7)	151/278	54.3	(48.3; 60.3)	207/370	55.9	(50.7; 61.1)	147/293	50.2	(44.3; 56.0)
Solicited systemic reaction	517/766	67.5	(64.0; 70.8)	169/278	60.8	(54.8; 66.6)	220/370	59.5	(54.3; 64.5)	167/293	57.0	(51.1; 62.7)
Unsolicited non-serious AE	336/768	43.8	(40.2; 47.3)	123/278	44.2	(38.3; 50.3)	169/370	45.7	(40.5; 50.9)	110/294	37.4	(31.9; 43.2)
Unsolicited non-serious AR	24/768	3 1	(2.0; 4.6)	5/278	1.8	(0.6; 4 1)	6/370	1.6	(0.6; 3.5)	5/294	1.7	(0.6; 3.9)
Grade 3 unsolicited non-serious AR	1/768	0 1	(0.0; 0.7)	0/278	0.0	(0.0; 1 3)	0/370	0.0	(0.0; 1.0)	0/294	0.0	(0.0; 1.2)
Anaphylactic reaction (SMQ)	0/768	0.0	(0.0; 0.5)	0/278	0.0	(0.0; 1 3)	0/370	0.0	(0.0; 1.0)	0/294	0.0	(0.0; 1.2)
Non-serious allergic reaction†	6/768	0.8	(0.3; 1.7)	1/278	0.4	(0.0; 2.0)	1/370	0.3	(0.0; 1.5)	3/294	1.0	(0.2; 3.0)
Post vaccination dengue-like syndrome	0/768	0.0	(0.0; 0.5)	0/278	0.0	(0.0; 1 3)	0/370	0.0	(0.0; 1.0)	0/294	0.0	(0.0; 1.2)
SAFETY ANALYSIS SET **Subjects experiencing at least one:**	**CYD (all) n/M**	**%**	**95% CI**	**Placebo (all) n/M**	**%**	**95% CI**	**Contol (all) n/M**	**%**	**95% CI**	**CYD Seropositive n/M**	**%**	**95% CI**
Discontinuation due to AE*	8/3233	0 2	(0.11; 0.49)	12/1505	0.8	(0.41; 1 39)	12/1597	0.8	(0.39; 1.31)	1/294	0.3	(0.01; 1.88)
Serious allergic reaction†	0/3233	0.0	(0.00; 0.11)	0/1505	0.0	(0.00; 0.24)	0/1597	0.0	(0.00; 0.23)	0/294	0.0	(0.00; 1.25)
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)	4/294	1.4	(0.37; 3.45)
SAE >28 days to 6 months post dose	181/3233	5.6	(4.83; 6.45)	105/1505	7.0	(5.74; 8.38)	110/1597	6.9	(5.69; 8.24)	17/294	5.8	(3.40; 9.10)
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)	0/294	0.0	(0.00; 1.25)
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)	0/294	0.0	(0.00; 1.25)
Death within 6 months	0/3233	0.0	(0.00; 0.11)	5/1505	0.3	(0.11; 0.77)	5/1597	0.3	(0.10; 0.73)	0/294	0.0	(0.00; 1.25)
Related death within 6 months	0/3233	0.0	(0.00; 0.11)	0/1505	0.0	(0.00; 0.24)	0/1597	0.0	(0.00; 0.23)	0/294	0.0	(0.00; 1.25)

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
* Identified in the termination form as SAE or other AE
† targeted list
SMQ: standard MedDRA query
Unsolicited non-serious AEs and ARs that occurred within the 28 days post-injection visit's time window (+14 days in most studies) were also included to provide a more comprehensive overview
Contributing studies: CYD14 CYD22 CYD23 CYD24 CYD28 CYD32
Source: Table 8 in Clinical Overview

In subjects aged 6 to 8 years regardless of baseline dengue serostatus, no immediate AEs were reported after any injection of the CYD dengue vaccine. Solicited reactions were reported in 76.5% of the Vaccine subjects (versus 70.5% in Placebo or Control subjects), and 5.9% of subjects experienced Grade 3 solicited reactions (compared to 9% of Placebo and 8.4% of Control subjects). In the CYD dengue vaccine Group, the most frequent solicited injection site reaction within 7 days after any CYD dengue vaccine injection was injection site pain (51.4% of subjects). Erythema (21.7%) and swelling (16.2%) were less frequently reported. The event rates in seropositive subjects who were in the

reactogenicity subset were generally similar to or lower than those in subjects 6-8 years of age regardless of baseline dengue serostatus.

Unsolicited non-serious AEs were reported in 43.8% of Vaccine subjects (44.2% of Placebo and 43.8% of Control). In addition, 3.1% of subjects reported at least 1 unsolicited non-serious adverse reaction (AR) and a single (0.1%) subject reported a Grade 3 reaction (vomiting). The most frequently reported unsolicited non-serious ARs were vomiting (0.9%), injection site hemorrhage, injection site induration, decreased appetite (0.4% each), and injection site bruising (0.3%).

There was a trend toward slightly higher incidence of solicited systemic reactions in the CYD dengue vaccine Group (67.5%) than in the Placebo Group (60.8%) or the Control Group (59.5%).

Overall, the safety profile of the CYD dengue vaccine in children aged 6 to 8 years was not different from the profile in children aged 9 to 16 years (See Table 46). The proportion of subjects reporting solicited reactions was similar in both age groups (76.5% of subjects aged 6 to 8 years and 73.7% of subjects aged 9 to 16 years) as well as the proportion of subjects reporting unsolicited non-serious ARs (3.1% of subjects aged 6 to 8 years, and 2.2% in subjects aged 9 to 16 years).

Table 46: Safety overview after any of 3 doses of CYD dengue vaccine or Placebo or Control, regardless of baseline dengue serostatus - Subjects 9 to 16 years - SafAS Main Studies Pooled

REACTOGENICITY SUBSET **Subjects experiencing at least one:**	**CYD n/M**	**%**	**95% CI**	**Placebo n/M**	**%**	**95% CI**	**Contol n/M**	**%**	**95% CI**
Immediate unsolicited AE	6/3666	0.2	(0.1; 0.4)	1/1152	<0.1	(0.0; 0.5)	3/1481	0.2	(0.0; 0.6)
Immediate unsolicited AR	3/3666	<0.1	(0.0; 0.2)	1/1152	<0.1	(0.0; 0.5)	1/1481	<0 1	(0.0; 0.4)
Grade 3 immediate unsolicited AR	1/3666	<0.1	(0.0; 0.2)	0/1152	0.0	(0.0; 0.3)	0/1481	0.0	(0.0; 0.2)
Solicited reaction	2687/3647	73.7	(72.2; 75.1)	824/1146	71 9	(69.2; 74 5)	1080/1474	73.3	(70.9; 75.5)
Grade 3 solicited reaction	403/3647	11.1	(10.1; 12.1)	105/1146	9 2	(7.6; 11.0)	141/1474	9.6	(8.1; 11.2)
Solicited injection site reaction	1883/3647	51.6	(50.0; 53.3)	497/1145	43.4	(40.5; 46 3)	717/1473	48.7	(46.1; 51.3)
Grade 3 solicited injection site reaction	56/3647	1.5	(1.2; 2.0)	11/1145	1.0	(0.5; 1.7)	21/1473	1.4	(0.9; 2.2)
Solicited systemic reaction	2387/3647	65.5	(63.9; 67.0)	754/1146	65.8	(63.0; 68 5)	977/1474	66.3	(63.8; 68.7)
Grade 3 solicited systemic reaction	380/3647	10.4	(9.4; 11.5)	104/1146	9 1	(7.5; 10.9)	133/1474	9.0	(7.6; 10.6)
Unsolicited non-serious AE	1496/3666	40.8	(39.2; 42.4)	480/1152	41.7	(38.8; 44.6)	651/1481	44.0	(41.4; 46.5)
Unsolicited non-serious AR	80/3666	2.2	(1.7; 2.7)	8/1152	0.7	(0.3; 1.4)	19/1481	1.3	(0.8; 2.0)
Grade 3 unsolicited non-serious AR	9/3666	0.2	(0.1; 0.5)	0/1152	0.0	(0.0; 0.3)	1/1481	<0 1	(0.0; 0.4)
Unsolicited non-serious injection site AR	43/3666	1.2	(0.9; 1.6)	5/1152	0.4	(0.1; 1.0)	9/1481	0.6	(0.3; 1.2)
Grade 3 unsolicited non-serious injection site AR	0/3666	0.0	(0.0; 0.1)	0/1152	0.0	(0.0; 0.3)	0/1481	0.0	(0.0; 0 2)
Unsolicited non-serious systemic AE	1484/3666	40.5	(38.9; 42.1)	478/1152	41 5	(38.6; 44.4)	649/1481	43.8	(41.3; 46.4)
Unsolicited non-serious systemic AR	39/3666	1.1	(0.8; 1.5)	3/1152	0 3	(0.1; 0.8)	10/1481	0.7	(0.3; 1.2)
Grade 3 unsolicited non-serious systemic AR	9/3666	0.2	(0.1; 0.5)	0/1152	0.0	(0.0; 0.3)	1/1481	<0 1	(0.0; 0.4)
Anaphylactic reaction (SMQ)	0/3666	0.0	(0.0; 0.1)	0/1152	0.0	(0.0; 0.3)	0/1481	0.0	(0.0; 0.2)

REACTOGENICITY SUBSET **Subjects experiencing at least one:**	**CYD n/M**	**%**	**95% CI**	**Placebo n/M**	**%**	**95% CI**	**Contol n/M**	**%**	**95% CI**
Non-serious allergic reaction (targeted list)	18/3666	0.5	(0.3; 0.8)	5/1152	0.4	(0.1; 1.0)	10/1481	0.7	(0.3; 1.2)
Non-serious Grade 3 allergic reaction (targeted list)	1/3666	<0.1	(0.0; 0.2)	0/1152	0.0	(0.0; 0.3)	0/1481	0.0	(0.0; 0.2)
Post-vaccination dengue-like syndrome	2/3666	<0.1	(0.0; 0.2)	0/1152	0.0	(0.0; 0.3)	0/1481	0.0	(0.0; 0.2)
SAFETY ANALYSIS SET **Subjects experiencing at least one:**	**CYD n/M**	**%**	**95% CI**	**Placebo n/M**	**%**	**95% CI**	**Contol n/M**	**%**	**95% CI**
Discontinuation due to AE*	78/197 15	0.4	(0.31; 0.49)	43/9163	0 5	(0.34; 0.63)	44/9492	0.5	(0.34; 0.62)
Serious allergic reaction (targeted list)	4/19715	<0.1	(0.01; 0.05)	1/9163	<0 1	(0.00; 0.06)	1/9492	<0 1	(0.00; 0.06)
SAE <=28 days post dose	127/19715	0.6	(0.54; 0.77)	70/9163	0.8	(0.60; 0.96)	76/9492	0.8	(0.63; 1.00)
SAE >28 days to 6 months post dose	547/19715	2.8	(2.55; 3.01)	299/9163	3 3	(2.91; 3.65)	314/9492	3.3	(2.96; 3.69)
Related SAE <=28 days post dose	4/19715	<0.1	(0.01; 0.05)	2/9163	<0.1	(0.00; 0.08)	2/9492	<0 1	(0.00; 0.08)
Related SAE >28 days to 6 months post dose	2/19715	<0.1	(0.00; 0.04)	0/9163	0.0	(0.00; 0.04)	0/9492	0.0	(0.00; 0.04)
Neurological disorder SAE <=30 days post dose	12/19715	<0.1	(0.03; 0.11)	8/9163	<0.1	(0.04; 0.17)	9/9492	<0 1	(0.04; 0 18)
Neurological disorder SAE >30 days to 6 months post dose	25/19715	0.1	(0.08; 0.19)	11/9163	0 1	(0.06; 0.21)	13/9492	0.1	(0.07; 0 23)
Death within 6 months post dose	5/19715	<0.1	(0.01; 0.06)	4/9163	<0 1	(0.01; 0.11)	4/9492	<0 1	(0.01; 0 11)
Related death within 6 months post dose	0/19715	0.0	(0.00; 0.02)	0/9163	0.0	(0.00; 0.04)	0/9492	0.0	(0.00; 0.04)

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
* Identified in the termination form as SAE or other AE
Contributing studies: CYD13 CYD14 CYD15 CYD22 CYD23 CYD24 CYD28 CYD30 CYD32 CYD65 CYD67 CYD71
Unsolicited non-serious AEs and ARs that occurred within the 28 days post-injection visit's time window (+14 days in most studies) were also included in the Safety Overview tables to provide a more comprehensive overview
Source: Table 2.7 in Summary of Clinical Safety

9.4.1 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 applicant.

9.4.2 Nonfatal Serious Adverse Events

From Table 45, SAEs within 28 days after any injection occurred in 41 (1.3%) subjects and a single (< 0.1%) subject experienced 1 SAE (neurological disorder SAE) assessed as related to the study vaccine by the Investigator (acute disseminated encephalomyelitis). The proportion of subjects who experienced at least 1 SAE was similar to that observed in the Placebo and Control Groups with 1.9% and 1.8% of subjects experiencing SAEs, respectively. Among the 181 subjects who reported SAEs between 28 days and 6 months post-injection in CYD vaccine group, none experienced a related SAE.

No related SAEs were reported during the long-term follow-up in subjects aged 6 to 8 years.

In baseline seropositive subjects, the incidences of SAE within 28 days after any of 3 doses in the CYD dengue vaccine, Placebo, and Control Groups were 1.4%, 1.8%, and 2.0%, respectively.

9.4.3 Study Dropouts/Discontinuations

The proportion of subjects who discontinued due to a non-serious AE or a SAE was 0.2% (8 subjects) in the CYD dengue vaccine Group compared to 0.8% (12 subjects) in the Placebo / Control Group.

9.4.4 Common Adverse Events

Please refer to the clinical reviewer's memo.

9.4.5 Clinical Test Results

Please refer to the clinical reviewer's memo.

9.4.6 Systemic Adverse Events

Solicited systemic reactions were reported by 67.5% of Vaccine subjects (compared to 60.8% of Placebo and 59.5% of Control subjects). The most frequently reported solicited systemic reaction was headache (51.5% of subjects) followed by malaise and myalgia. Most solicited systemic reactions were Grade 1, occurred within 3 days after injection (except for fever, which appeared throughout the solicited period) and lasted between 1 and 3 days. In the Placebo and Control Groups, the incidence of each solicited systemic reaction tended to be similar (fever, headache, and asthenia) or lower (malaise and myalgia) to that reported in the CYD dengue vaccine Group. However, the percentage of subjects who experienced each Grade 3 solicited systemic reaction tended to be lower in the Vaccine group compared to the Placebo or Control group. The proportion of subjects reporting solicited systemic reactions was similar in subjects aged 6 to 8 years (67.5%) and in subjects aged 9 to 16 years (65.5%).

9.4.7 Local Reactogenicity

Solicited injection site reactions were reported in approximately half of the subjects (56.1%). The most frequently reported solicited injection site reaction was injection site pain (51.4% of subjects). Most solicited injection site reactions were Grade 1, occurred within 3 days after injection and lasted between 1 and 3 days of occurrence. Grade 3 solicited injection site reactions were reported by fewer subjects (0.4%). The frequency of each solicited injection site reaction was similar in the Placebo and Control groups. The proportion of subjects reporting solicited injection site reactions tended to decrease slightly when age increased (56.1% of subjects aged 6 to 8 years and 51.6% of subjects aged 9 to 16 years).

9.4.8 Adverse Events of Special Interest

Please refer to the clinical reviewer's memo.

9.5 Additional Safety Evaluations

NA

9.6 Safety Conclusions

The reactogenicity profile of the CYD dengue vaccine in subjects aged 6 – 8 years in terms of incidence, severity, and nature of events was generally similar to that reported after injection of placebo or comparator vaccine, and was comparable to that of the 9 – 16 years old subjects. The reactogenicity profile of vaccinated baseline seropositive subjects 6-8 years of age was generally similar to that of subjects 6-8 years of age regardless of baseline serostatus. SAEs within 28 days after any injection were reported in approximately 1.3% of subjects in the CYD vaccine group and 1.9% in the placebo group. These rates were slightly higher overall than those in the 9 – 16 years old subjects. Deaths were reported only in the Placebo or Control Group and no deaths were assessed as related to the study vaccine.

10. Additional Statistical Issues

NA

11. Conclusions

The results across the statistical methods were consistent, and the totality of data would likely support efficacy of the CYD dengue vaccine against symptomatic VCD in 6- to 8-year-old seropositive children. Results did not reveal evidence of increased risks of hospitalized VCD and severe VCD in seropositive children 6 to 8 years of age. No major new safety issues with the proposed age group were discovered from a statistical perspective. The reactogenicity profile from the baseline seropositive children aged 6 to 8 years appeared similar to that of children aged 9 to 16 years.