Application Type	Original BLA Submission
STN	STN 125682/0
CBER Received Date	August 31, 2018
PDUFA Goal Date	May 01, 2019
Division / Office	Division of Vaccines and Related Product Applications (DVRPA) Office of Vaccines Research and Review (OVRR)
Committee Chair	Kirk Prutzman, PhD
Clinical Reviewer(s)	Ralph LeBlanc, MD, PhD
Project Managers	Ramchandra Naik, PhD Stephanie Polo
Priority Review	Yes
Reviewer Name(s)	Mridul K. Chowdhury, PhD VEB/DB/OBE
Review Completion Date / Stamped Date	April 30, 2019
Concurrence	Lei Huang, PhD Concurring Reviewer, Vaccine Evaluation Branch (VEB), Division of Biostatistics (DB), Office of Biostatistics and Epidemiology (OBE)
	Tsai-Lien Lin, PhD Branch Chief, VEB/DB/OBE
	John Scott, PhD Director, DB/OBE
Applicant	Sanofi Pasteur, Inc.
Proper Name	Dengue Tetravalent Vaccine, Live Suspension for Subcutaneous Injection
(Proposed) Trade Name	DENGVAXIA
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), for use in 9 through 16 years old subjects.
Indication(s) and Intended Population(s)	DENGVAXIA is a vaccine indicated for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4. DENGVAXIA is indicated for use in individuals 9 through 16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas. Limitations of use: • DENGVAXIA is not for use in individuals not previously infected by any dengue virus serotype or for whom this information is unknown. Those not previously infected are at increased risk for severe dengue disease when vaccinated and subsequently infected with dengue virus. Previous dengue infection can be assessed through a medical record of a previous laboratory-confirmed dengue infection or through serological testing prior to vaccination. • The safety and effectiveness of DENGVAXIA have not been established in individuals living in dengue non-endemic areas who travel to dengue endemic areas.

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Glossary

1/dil	reciprocal of dilution
Ab	antibody
AP	Asia Pacific
BLA	biologics license application
CBER	Center for Biologics Evaluation and Research
CDP	Clinical Development Program
CI	Confidence interval
CYD	Chimeric Yellow Fever Dengue
DF	dengue fever
DHF	dengue hemorrhagic fever
ELISA	enzyme-linked immunosorbent assay
FASE	full analysis set for efficacy
FASSEP	full analysis set for surveillance expansion phase
FASI	full analysis set for immunogenicity
FDA	Food and Drug Administration
FV	flavivirus
GMT	Geometric mean titer
GMTR	Geometric mean of titer ratio
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee

ISE	integrated summary of efficacy
ITT	intent-to-treat
LatAm	Latin America
LLOQ	lower limit of quantitation
mFASE	modified full analysis set for efficacy
NS1	non-structural 1
PoC	proof of concept
PPSE	per-protocol analysis set for efficacy
PRNT	plaque reduction neutralization test
RMP	Risk Management Plan
RT-PCR	reverse transcription-polymerase chain reaction
SVCD	severe virologically-confirmed dengue
VCD	virologically-confirmed dengue
VE	vaccine efficacy
VRBPAC	Vaccines and Related Biological Products Advisory Committee
WHO	World Health Organization
YF	yellow fever

1. Executive Summary

1.1 Introduction

Sanofi Pasteur submitted the original Biologics License Application (BLA) STN 125682/0 for licensing the Dengue Tetravalent Vaccine (Live, Attenuated) on August 31, 2018. The vaccine is 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 (ref. section 5.4.1 for additional information) with laboratory-confirmed previous dengue infection and living in endemic areas. CBER granted a priority review designation for the BLA because of the global outbreaks of dengue virus infection.

There were two large-scale pivotal Phase III studies:

- CYD14 conducted in Asia Pacific (AP) countries with 10,275 healthy subjects aged 2-14 years randomized in 2:1 to the CYD vaccine and placebo groups, and
- CYD15 conducted in Latin America (LatAm) with 20,869 healthy subjects aged 9-17 years randomized in 2:1 to the CYD vaccine and placebo groups

Based on these studies, the BLA reports that the estimated overall primary vaccine efficacy (VE) against virologically confirmed dengue (VCD) cases during the 12-month time period from 28 days post dose 3, due to any serotype and severity, was 56.5% (95% CI: 43.8, 66.4) in pivotal study CYD14 and 60.8% (95% CI: 52.0, 68.0) in pivotal study CYD15. The vaccine was administered in three doses at 6 months apart. The period from month 0 of initial dose to month 25 was designated as Active Phase of surveillance, while the period from 28 days post-dose 3 to end of Active Phase (i.e., month 25) was used to determine the primary efficacy endpoint (Figure 1). Each study met its pre-specified success criterion, as the 2-sided 95% CI lower bound for VE was above the pre-specified limit of 25%. More details follow in Table 2, Table 8, and Table 17.

During clinical development, excess risk for dengue diseases and related hospitalization was noted in subjects who were younger (< 9 years old) and/or did not have previous dengue infection. As a risk mitigation step, these populations are not included in the proposed indication. The submission also included immunogenicity bridging of the pivotal efficacy subjects to adult subjects (18-45 years old) in order to extrapolate efficacy for adults. The adults, although dengue seropositive at baseline, were chosen post-hoc from non-pivotal studies that did not have design pre-specifications and adequacy of sample sizes to enable the type of immunogenicity comparisons needed for bridging, thus rendering the comparison inadequate to draw firm conclusions. At the Vaccines and Related Biological Products Advisory Committee (VRBPAC) (March 7, 2019), reservations were expressed about the bridging studies. The Committee voted that efficacy had been demonstrated in individuals 9 through 16 years of age but did not recommend extending the indication to adults based on the bridging studies. In a recent Amendment STN 125682/0/42 dated April 8, 2019, the applicant amended the proposed indication to be confined to individuals ages 9 through 16 years. This statistical report encompasses my review of the BLA as it was originally submitted, including the bridging study.

1.2 Brief Overview of BLA Submission

The clinical development program (CDP) of the CYD dengue vaccine was conceived to address the medical need for a vaccine in dengue endemic regions. At the time of CDP, there was no licensed dengue vaccine, nor was any immunological correlate of protection established. Therefore, efficacy of the CYD dengue vaccine was assessed in endemic areas -- initially as a proof of concept (PoC) phase IIb study in 1 center in Thailand (CYD23) and subsequently in 2 large-scale, statistically powered, pivotal phase III studies conducted in 10 countries of Asia Pacific (CYD14) and Latin America (CYD15). The CDP included several studies. The Applicant referred to two phase III studies CYD14 and CYD15 as "pivotal studies" while all others (phase II and III) were designated as "supportive studies" (ref. Summary of Clinical Efficacy, page 20 of 358). This review includes the two pivotal studies and selected supportive studies (including CYD17 which was phase III for lot-consistency) contributing to package insert information. These studies are listed in Table 1 and Table 14, with further details appearing in the texts that follow.

Overall, the submitted results supported that the primary efficacy objective was met. The results also showed persistence of immunogenicity post-dose 3 for all 4 serotypes. Lot consistency criteria were satisfied, except for one comparison of Lot1 vs Lot2 for serotype 2, where the upper confidence limit of 0.340 on log10GMT difference exceeded 0.301, the pre-specified limit.

1.3 Major Statistical Issues and Conclusions

Studies CYD14 and CYD15 each included tests of the null hypothesis H_0: VE $\leq$ 25% against the alternative hypothesis H_1: VE > 25%. The pre-specified study success criteria required the lower bound of the 2-sided 95% CI for VE to exceed 25%. This criterion was met in both studies. The studies were powered for overall VE of any serotype, not for individual VEs by serotype. Section 6.1.8 provides further details. Covariate effects on VCD cases were evaluated by logistic regression models (Table 24). In the regression models as applied on CYD14 and CYD15 integrated data, the VCD incidence was reduced in the CYD dengue vaccine group, and showed a tendency to be lower with increased titer. The regression models, however, may not have good predictive power (ref. last row, Table 24). Further details follow in point 7 of section 7.3. The reduction in VCD cases with CYD dengue vaccine and with higher titer can also be seen in Table 23. Section 7.2 describes and discusses this table.

The results as a whole, including the data in Table 23 and the statistical significance of the vaccine group effect in the logistic regression analysis, suggest that a high titer alone does not completely predict vaccine efficacy. This speaks against using bridging of immunogenicity of the 9-17 years old subjects in pivotal studies (CYD14/CYD15) with that of adults aged 18-45 years in selected phase II studies (CYD22/CYD28/CYD47) to conclude efficacy in the adult population. This is in addition to the limitations of the bridging studies themselves, including the lack of pre-specification and inadequate sample size.

The quality of the submission was sufficient for statistical evaluation.

1.4 Summary Results

1. Overall, the primary objective was met in both pivotal studies. The analyses demonstrated vaccine efficacies of 56.5% (95%CI: 43.8; 66.4) in pivotal study CYD14 and 60.8% (95% CI: 52.0; 68.0) in pivotal study CYD15. Integrating these two studies, the CYD vaccine was associated with an overall reduction of 59.2% (95%CI: 52.3; 65.0) in VCD incidences due to any serotype post-dose 3. The lower confidence bounds of VE exceeded the pre-specified 25% limit, establishing efficacy.

2. The CYD dengue vaccine also reduced overall incidences of VCD during the whole Active Phase (Day 0 to Month 25). The VEs in individual studies CYD14 (subjects aged 2-14 years) and CYD15 (9-16 years) were 54.8% (95% CI: 46.8; 61.7) and 64.7% (95% CI: 58.7; 69.8), respectively, and 60.3% (95% CI: 55.7; 64.5) after integration (Table 18).

3. The reduction of VCD incidences was observed in post-dose 3 period and in the whole Active Phase period, in different serotypes. For serotypes 1 and 2, however, some of the lower confidence bounds were negative or below the 25% limit (Table 3 and Table 9).

4.The VEs were, overall, higher in baseline dengue immune subjects compared to the baseline dengue non-immune subjects (Table 4 and Table 10), where baseline immune status is defined as titers ≥ 10 (l/dil) against at least one dengue serotype at baseline. For the baseline dengue immune versus non-immune subjects, the VEs (95% CI) post-dose 3 from integrated results were respectively 79.4% (58.4; 89.8) and 42.7% (-41.1; 76.8) in subjects aged 9-16 years (Table 19). For the same comparison during the Active Phase, the corresponding VEs (95% CI) were 81.9% (67.2; 90.0) and 52.5% (5.9; 76.1), respectively (Table 20).

5. The VEs against VCD post dose 3 appeared to have varied by subject age, with estimates of 45.7% (95% CI: 17.2;64.3) for age 2-5 years (CYD14), 56.2% (95% CI: 45.9; 64.5) for age 6 – 11 years, and 68.7% (95% CI: 59.1;76.0)for 12-16 years, based on CYD14+CYD15 integrated results (Efficacy Integrated Analysis Report, Table 3.4.5.1, Page 180 of 1365). The observed age pattern more or less also held in the Active Phase (Figure 3). Although the point estimates of VE increase with age, it is worth noting that the confidence intervals for these estimates substantially overlap.

6. The CYD vaccine reduced hospitalized VCD cases by 78.6% (95% CI: 57.0; 90.0) in the post-dose 3 period and 80.3% (95% CI: 65.0; 89.0) in the Active Phase period, in CYD15. In CYD14, these respective VEs were 71.4% (95% CI: 49.0;84.0) and 67.0% (95% CI: 50.0;79.0). A reduction was also seen in VCD cases meeting WHO criteria, with VE ≥ 80% regardless of periods and in both pivotal studies.

7. The GMTs in CYD vaccinees increased from pre-injection 1 level to post-injection 2 and to post-injection 3 for all 4 serotypes. During the first year post-dose 3 and in subsequent years, the GMTs declined, but maintained a higher level than baseline and than the level demonstrated by Control subjects. Additionally, the proportion of subjects seropositive (i.e., titers ≥ 10(1/dil)) at 4 years post-dose 3 persisted at high levels regardless of serotype. The seropositive rates ranged from 79.2% to 89.6% in CYD14 and from 88.7% to 94.2% in CYD15, for all serotypes.

8. Post-dose 3 GMT was influenced by baseline dengue immune status. The post-dose 3 GMTs were higher among baseline dengue immune subjects compared to those who were dengue non-

immune at baseline. Such influence coupled with increased exposure with age can make GMT increase with age, a pattern shown in Figure 4.

9. Lot consistency criteria were satisfied for 11 out of 12 comparisons (3 lots and 4 serotypes). For the comparison of Lot 1 vs Lot 2 for serotype 2, the upper confidence limit of 0.340 on log10titer difference exceeded 0.301, the pre-specified limit. In other words, the GMT ratio's upper confidence limit of $10^{0.34} = 2.188$ was above the pre-specified 2-fold change. Whether the finding has any clinical or safety concern is deferred to the clinical/product reviews.

1.5 Conclusion/Recommendation

Overall, based on the pivotal studies, the primary efficacy objective was met.

2. Clinical and Regulatory Background

Please refer to the medical officer's review.

3. Submission Quality and Good Clinical Practices

3.1 Submission Quality and Completeness

The quality of the submission was sufficient to enable a statistical evaluation.

3.2 Compliance with Good Clinical Practices and Data Integrity

No data integrity issues with respect to efficacy or immunogenicity data in the pivotal studies were noted.

4. Significant Efficacy/Safety Issues Related to Other Review Disciplines

Deferred to other discipline reviewers.

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

5.1 Review Strategy

The statistical review of this BLA comprises of two parts: efficacy and immunogenicity were reviewed by Dr. Chowdhury; safety and assay/CMC were reviewed by Dr. Huang.

This submission included the clinical study reports of Protocols CYD14 and CYD15. These two were the pivotal efficacy studies to support approval of the BLA and were reviewed. Statistical aspects of immunogenicity and lot-to-lot consistency of the lot-consistency study CYD17 were reviewed.

5.2 BLA Documents that Serve as the Basis for the Statistical Review

The submission (STN 125682/0) was received on August 31, 2018. The Amendment STN 125682/0/42 requesting change in age indication (from 9-45 years to 9-16 years) arrived on April

8, 2019. These are located in the EDR. The clinical study reports, electronic data sets, and other related materials including SAP are included in modules 2 and 5 of the BLA.

5.3 Overview of Clinical Trials/studies

Please refer to section 1.2 for overview of the clinical development program and studies. A summary of the basic information about phase III studies is included in Table 1.

Table 1: General Information about Phase III Studies

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 vaccn: 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) (coded CYD57)	Proof of concept Phase IIb, randomized, controlled, blind-observer, 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
CYD17 (Australia, Non-endemic area) 05 Oct 2010 to 12 Jun 2012 6 month post injection 3 safety follow-up	Phase III, randomized, placebo controlled, blind-observer, multicenter trial, primarily to evaluate - Lot-to-lot consistency (based on GMTs 28 days post-dose 3) across 3 Phase III lots - Bridging between Phase II and Phase III lots - Descriptive safety, after each injection Randomized in groups: Groups 1, 2 and 3: CYD dengue vaccine (~5 log10CCID50/ serotype 1, 2, 3, 4) Phase III lots 1, 2, 3 respectively at D0, M6 and M12 Group 4: CYD dengue vaccine Phase II lot at D0, M6 and M12 Group 5: Placebo (NaCl 0 9%) at D0, M6 and M12 0 5 mL/ injection Subcutaneous injection	Healthy subjects 18-60 years old Randomized: 715 (CYD Phase III lots: Group1,Group2, Group3), CYD Phase II lot: Group 4 Placebo: Group 5 - Group 1: 164 - Group 2: 163 - Group 3: 163 - Group 4: 168 - Group 5: 57	Lot consistency were criteria satisfied, except for one comparison involving serotype 2 and lot1-lot2, where the confidence upper limit of 0 340 on log10GMT differences exceeded 0 301, the pre-specified limit

*Source Summary of Clinical Efficacy, Table 1 (pages 28, 33), Table 16 (page 136)***.**

5.4 Consultations

5.4.1 Advisory Committee (VRBPAC)

The VRBPAC Meeting was held on March 7, 2019. The Committee did not recommend basing an indication on the Applicant's proposed immunogenicity bridging between adult subjects aged 18 through 45 years and study's pivotal efficacy subjects aged 9 through 16 years. The concern was that the available immunogenicity data of adults offered only descriptive comparison with that of the pivotal efficacy subjects. The adults' data were not collected through design pre-specification required for valid statistical comparison of immunogenicity. The Committee voted that efficacy was demonstrated for the limited age range of 9 through 16 years of subjects, based on the two pivotal studies.

6. Discussion of Individual Studies/Clinical Trials

6.1 Pivotal Study #1: Protocol CYD14

Title: Efficacy and Safety of a Novel Tetravalent Dengue Vaccine in Healthy Children Aged 2 to 14 years in Asia- Interim clinical study report up to 48 months after the third injection.

6.1.1 Objectives

Primary Objective:

To assess the efficacy of CYD dengue vaccine after 3 vaccinations at 0, 6 and 12 months in preventing symptomatic virologically-confirmed dengue cases, regardless of the severity, due to any of the 4 serotypes in children aged 2 to 14 years at the time of inclusion.

Primary Endpoint: Symptomatic virologically-confirmed dengue (VCD) cases occurring > 28 days after Dose 3 (during the Active Phase) and defined as:

- Acute febrile illness (i.e., temperature ≥ 38°C on at least 2 consecutive days)
- Virologically-confirmed by dengue RT-PCR and/or dengue NS1 ELISA Ag Test

The Applicant stated that "It was expected that the number of cases of symptomatic dengue that were virologically confirmed in a 12-month period were sufficient to demonstrate efficacy. As this period began after 28 days after Dose 3, the Active Phase of dengue surveillance continued for each subject until 13 months after Dose 3."

Secondary Objectives (selected):

Efficacy during Active Phase

To describe the efficacy of CYD dengue vaccine in preventing symptomatic virologically-confirmed dengue cases after the third dose to the end of the Active Phase:

- due to each of the 4 serotypes.

Immunogenicity Subset **(N=2000)**

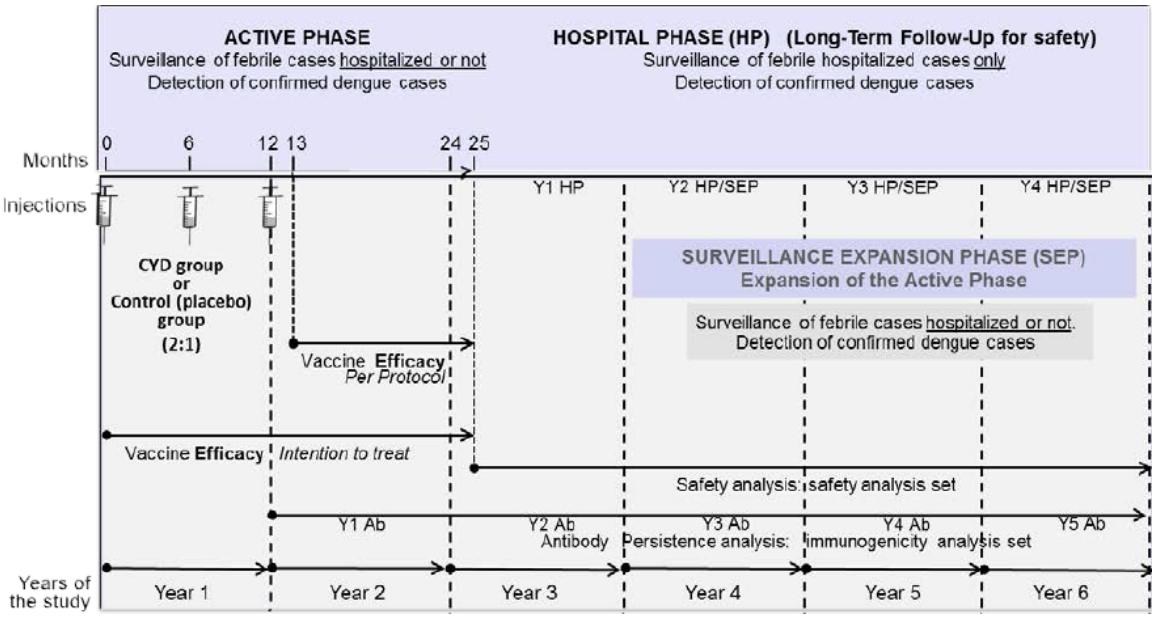
To describe the Ab response to each dengue serotype after Dose 2, after Dose 3, and 1, 2, 3, 4 and 5 years after Dose 3.

Safety Objective:
Deferred to Safety Review by Dr. Huang.

6.1.2 Design Overview

Study CYD14 was a randomized, observer-blind, placebo-controlled, multicenter clinical trial. A total of 10,275 healthy children aged 2-11 years and adolescents aged 12-14 years were enrolled and randomized in 2:1 to the CYD vaccine group and placebo (NaCl 0.9%) control, respectively. In both groups, 3 injections were administered at 6-month apart with a time window of ± 20 days for the second and third injections. A subset of subjects from each country was evaluated for immunogenicity, reactogenicity and baseline dengue and JE Ab levels. This immunogenicity subset included a total of 2000 subjects, of which 1333 were in the CYD dengue group and 667 were in the control group. Dengue cases were captured by active surveillance. The applicant considered that the number of symptomatic dengue cases virologically confirmed in a 12-month period was sufficient to demonstrate efficacy. As this period began after 28 days after Dose 3, the Active Phase of dengue surveillance continued for 13 months after Dose 3. Active phase was followed by surveillance to detect hospitalized dengue cases. After one year of hospital phase, subjects who consented for expanded surveillance were actively followed and those declined consent continued the hospital phase until trial completion (up to 60 months post-dose 3) (Figure 1).

Figure 1: Outline of trial design



Source. Clinical Overview, page 15 of 120.

6.1.3 Population

Healthy Subjects, 2–14 years old.
Randomized: 10,275
CYD vaccine: 6851
Placebo: 3424

For inclusion and exclusion criteria, please refer to Clinical Reviewer report.

6.1.5 Sites and Centers

Study CYD14 was conducted in 11 centers in Indonesia, Malaysia, Philippines, Thailand and Viet Nam.

6.1.6 Surveillance/Monitoring

Deferred to clinical reviewer's review.

6.1.7 Endpoints and Criteria for Study Success

Please refer to section 6.1.1 above for the primary and secondary endpoints.

With the primary objective to assess the efficacy of the CYD dengue vaccine (VE) after 3 injections in preventing the occurrence of symptomatic VCD cases, statistical methodology (ref. section 6.1.8) required that, for study success, the 2-sided 95% CI lower bound for VE exceed 25%, the pre-specified margin.

6.1.8 Statistical Considerations and Statistical Analysis Plan

Statistical hypotheses tested (primary endpoint)
The primary objective was to establish the efficacy of the CYD dengue vaccine. The following hypotheses for vaccine efficacy (VE) were tested using an alpha=2.5% and >90% power (SAP, section 5.4, page 64).

$$H_0: VE \leq 25\%, H_1: VE > 25\%$$

The statistical methodology was based on the use of the two-sided 95% CI of VE. The CI was calculated using the exact method [Breslow NE, Day NE. *Statistical methods in cancer research. Volume II: The design and analysis of cohort studies.* Oxford (UK): Oxford University Press; 1987.]
For study success, the criterion required the lower bound of the 2-sided 95% CI of VE to exceed 25%.

The primary analysis was performed using the per-protocol analysis set for efficacy (PPSE). The analysis on modified full analysis set (mFASE) was used as supportive (SAP, section 5.2.2, page 58).

Statistical Methods (primary endpoint)

The vaccine efficacy (VE) of the CYD vaccine was estimated by:

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

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

where:

P_{CYD} is the density incidence of dengue in the CYD Dengue Vaccine Group

P_P is the density incidence of dengue in the Control Group

C_{CYD} is the number of subjects with at least one symptomatic virologically-confirmed dengue case (whatever the serotype) between 28 days post-Dose 3 and the end of the Active Phase in the CYD Dengue Vaccine Group

N_{CYD} is the number of person-years in the CYD Dengue Vaccine Group

C_P is the number of subjects with at least one symptomatic virologically-confirmed dengue case (whatever the serotype) between 28 days post-Dose 3 and the end of the Active Phase in the Control Group

N_P is the number of person-years in the Control Group

Person-years are the sum of individual units of time (years) for which the subjects contributed to the analysis. This is equal to the person-time (in days) at risk divided by 365.25.

For subjects with several episodes of dengue, only the first virologically-confirmed dengue case occurring after 28 days post-Dose 3 was considered in the analysis of the VE against any serotype.

The formula for VE can be rewritten as

$$VE = 100 \times \left[1 - \frac{N_P}{N_{CYD}} \times \frac{q}{1-q}\right]$$

where $q = C_{CYD} / (C_{CYD} + C_P)$, i.e., proportion of cases who received CYD dengue vaccine. This makes $q/(1-q) = C_{CYD} / C_P$. Conditionally on the total number of cases, C_{CYD} follows binomial distribution $(q, C_{CYD} + C_P)$. The ratio $q/(1-q)$ being increasing function of q, a CI for q can be transformed into the CI for VE (ref. SAP, page 41 of 129 and citations listed).

To explore association between Ab level and dengue occurrence, the logistic regression and vaccine efficacy curve (VE) approaches were used by the Applicant. The logistic regression studied association of PRNT50 titers with the probability of dengue disease, and the VE curve approach explored the increasing pattern of VE with average PRNT50 titer. While these analyses were exploratory, the results from the commonly used logistic regression method will mainly be referred to in this review.

Analysis Populations

Following are the main descriptions from the Applicant (SAP, page 56).

a. Per-Protocol Analysis Set

The per-protocol (PP) analysis sets will include all subjects who had no protocol deviations.

Per-Protocol Analysis Set for Efficacy

Subjects will be excluded from the per-protocol analysis set for efficacy (PPSE) for the following reasons:

- Subject did not meet at least one of the protocol-specified inclusion/exclusion criteria and did not respect the definite contraindications
- Subject did not receive the correct number of injections
- Subject received at least one dose of a product other than the one that he/she was randomized to receive
- Administration of vaccine was not done as per-protocol (site and route of administration)
- Subject did not receive vaccine in the time window defined in the table of study procedures
- Subject received a protocol-restricted therapy or vaccine from Category 2
- Subject with an emergency unblinding performed by the Investigator
- Subject did not have at least one contact point after 28 days post-Dose 3 and before the end of the Active surveillance period

Subjects will remain in this population until meet one of the above criteria. The PPSE set will be used for the analysis of VE from 28 days post-Dose 3 to the end of the Active Phase.

Per-Protocol Set for Immunogenicity

The per-protocol set for immunogenicity (PPSI) will include subjects from the immunogenicity subset.

Subjects will be excluded from the PPSI for the following reasons:

- Subject did not meet at least one of the protocol-specified inclusion/exclusion criteria and did not respect the definite contraindications
- Subject did not receive the correct number of injections
- Subject received at least one dose of a product other than the one that he/she was randomized to receive
- Administration was not done as per-protocol (site and route of administration)
- Subject did not receive vaccine in the time window defined in the table of study procedures
- Subject did not provide at least one post-dose serology sample in the time window defined in the Table of Study Procedures (after 2nd and 3rd injection)

- Subject's post-vaccination serology sample did not produce a valid test result (i.e., a result different from "not-reportable" ['NR'] or missing, for at least one dengue serotype).
- Subject received a protocol-restricted therapy or vaccine from Category 2

Subjects will remain in each population as long as they do not meet one of the above criteria, except for blood sample timing. The PP set will be used and adapted to the analysis of immunogenicity pre- and post-injection (i.e., 3 PPSI populations).

b. Full Analysis Set

Full Analysis Set for Efficacy (FASE)
The FASE will include all subjects who received at least one injection

Modified Full Analysis Set for Efficacy (mFASE)

The mFASE will include all subjects who received 3 injections, regardless of the per-protocol criteria.

Full Analysis Set for Immunogenicity (FASI)

The FASI is defined as the subjects of the immunogenicity subset who received at least one injection and who had a blood sample drawn and a result available after this injection.

Titer measurements"Titer reported as < LLOQ will be converted to a value of ½LLOQ. For calculating geometric mean of titer ratio (GMTR), < LLOQ will be converted to ½LLOQ for a numerator and < LLOQ will be converted to LLOQ for a denominator. There is no upper limit of quantification (ULOQ) with the PRNT method planned." (SAP, Page 26/129).

Two key periods for VE calculation
Post-Dose 3: from 28 days post-dose 3 to the end of the Active Phase (**primary endpoint**).
Active Phase: from Day 0 (D0) to the end of the Active Phase.
(ref. SAP, Page 22/129)

6.1.9 Study Population and Disposition

Demographic characteristics at baseline

A total of 10,275 healthy subjects aged 2-14 years were randomized at a 2:1 ratio, with stratification by site and age (2 to 5 years, 6 to 11 years and 12 to 14 years), to either the CYD vaccine group (N=6851) or the control group (N=3424). The distribution by country of the randomized subjects was the following: Indonesia 1870, Malaysia 1401, Philippines 3501, Thailand 1170, and Vietnam 2333. A total of 2000 subjects were randomized in the immunogenicity subset. Females were about 52% of the subjects in both study groups. Also, overall, 24.0% of the subjects were in the age group 2 to 5 years old, 53.3% in the age group 6 to 11 years old, and 22.8% in the age group 12 to 14 years old. In the immunogenicity subset, seroprevalence for dengue was about 67.5% in both CYD vaccine and control groups (CSR CYD14, page 51, 52), but it varied by age with highest being 81.0% at age 12 to 14 years, followed by 71.8% at age 6 to 11 years and 51.3% at age 2 to 5 years (CSR CYD14, page 176 of 1568).

Disposition

Overall, out of 10,275 subjects randomized, 10,194 subjects completed the Active phase (99.2%), 10,272 received the first injection, 10,190 received the second injection and 10,151 received the third injection, and in each of these dispositions the dengue vaccine to control ratio of subjects remained at around 2:1 as planned. Additionally, for per-protocol efficacy set, 6709 subjects were analyzed for the dengue vaccine arm as against 3350 subjects in the controlarm, again maintaining the ratio at around 2:1. Overall, the subjects displayed high compliance rate in both study groups, and a concern for imbalance from the planned ratio of assignment was not discerned. The applicant provided further details in Appendix 1.

6.1.10 Efficacy Analyses

6.1.10.1 Analyses Results

Primary Objective

VE against VCD due to any serotype and severity. The study reported during Active Phase a total of 612 febrile episodes as being virologically-confirmed dengue episodes, with 293 in the CYD group and 319 in the Control group. The distinct number of subjects (i.e., VCD cases) are presented, first for post-dose 3 (PD3) in Table 2 (primary analysis, a total of 250 cases, PPSE) and in Table 3 for PD3 and Active Phase regardless of serotypes and for each serotype. From Table 2, the overall primary estimate of vaccine efficacy PD3 due to any serotype and severity was 56.5%. The 2-sided 95% CI lower bound was 43.8%, which exceeded the pre-specified VE limit of 25%, thus meeting the success criterion.

Table 2: Vaccine Efficacy Against VCD Due to Any Serotype – Post-Dose 3, PPSE

	CYD Dengue Vaccine Group (N=6709)				Control Group (N=3350)				Vaccine Efficacy	
	Cases	Person-years at risk	Density incidence (95% CI)	n Episodes	Cases	Person-years at risk	Density incidence (95% CI)	n Episodes	%	(95% CI)
Symptomatic VCD	117	6525	1.8 (1.5; 2.1)	117	133	3227	4.1 (3.5; 4.9)	134	56.5	(43.8;66.4)

Cases: number of subjects with at least one symptomatic VCD episode from 28 days post-injection 3 to the end of Active Phase.
Density incidence: data are cases per 100 person-years at risk.
The person-years at risk was the cumulative time (in years) until the participant was diagnosed with VCD or until the end of the active period, whichever came first. The person-years at risk calculation presented in the tables is the sum of individual units of time for which the participants contributed to the analyses. Incidence density was calculated as the number of VCD cases divided by the cumulative person-years at risk.
n Episodes: number of symptomatic VCD episodes in the considered period.
Source: CSR CYD14, page 179 of 1568.

Secondary Objectives

1. VE *by Serotype*. Similar PD3 results as above for VE were obtained from mFASE population as well (Table 3). From serotype-specific descriptive analyses, the post-dose3 VE estimates ranged from 35.0% to 78.4%, with confidence LB of -9.2% for serotype 2 displaying only limited efficacy performance compared to other serotypes. For Active Phase as well, the VE estimate for serotype 2 was lowest at about 35% with confidence LB of 10.4%, which is described as being considerably lower than the 25% limit.

Table 3: VE against VCD due to any and each serotype, post-Dose 3 and during the Active Phase

	Post-Dose 3			Active Phase		
	Number of cases CYD vs Control	**VE (%)**	**(95% CI)**	**Number of cases CYD vs Control**	**VE (%)**	**(95% CI)**
Any serotype	118/134	56.5	(43.8; 66.3)	286/309	54.8	(46.8; 61.7)
Serotype 1	51/50	50.0	(24.6; 66.8)	116/126	54.5	(40.9; 64.9)
Serotype 2	38/29	35.0	(-9.2; 61.0)	97/74	34.7	(10.4; 52.3)
Serotype 3	10/23	78.4	(52.9; 90.8)	30/43	65.2	(43.3; 78.9)
Serotype 4	17/34	75.3	(54.5; 87.0)	40/72	72.4	(58.8; 81.7)

Cases: number of subjects with at least one symptomatic VCD episode in the considered period.
Post-Dose 3: period from 28 days post-Dose 3 to the end of the Active Phase (mFASE)
Active Phase: period from Day 0 to the end of the Active Phase (FASE)
Source: Adapted from CSR CYD14, page 53 of 1568.

2. Hospitalization with VCD cases

Post-Dose 3, a total of 55 subjects, 20 in CYD Vaccine Group and 35 in Control Group, were hospitalized with VCD, thus reporting a VE of 71.4% (95% CI: 49.0;84.0), which is an overall reduction of more than 71% in the incidence of hospitalization with dengue cases in the CYD vaccine group compared to Control.
Active Phase also reported corresponding reduction of 67% (95% CI: 50.0;79.0). A total of 101 subjects with VCD reported hospitalization, 40 in the CYD Dengue Group and 61 in the Control Group (CSR CYD14, page 54).

3. WHO Criteria and VCD Cases

Post-dose 3, 16 subjects reported VCD episodes due to any serotype and that met WHO criteria. During Active Phase, 28 subjects reported episodes that met WHO criteria. Overall, the VEs were 88.5% (95% CI: 58.2;97.9) and 80.0% (95% CI: 52.7;92.4) for the two periods, respectively (CSR CYD14, page 54).

4. VE and Covariates

From Table 4, VE appeared to have increased from 33.6% at 2-5 years of age to 67.8% at 9-14 years of age, during Active Phase. The increase in VE with age was noted in PD3 as well (CSR CYD14, page 210 of 1568). In both of the CYD vaccine and Control groups, the VCD incidence was highest in the youngest age group. Despite increase from the youngest age group, the VEs in the subsequent two higher age groups did not have a marked increasing trend. Considering the immunogenicity subset only, where baseline dengue status data were collected, the dengue immune subjects showed VCD relative risk of 0.257 (95% CI: 0.14; 0.47) compared to 0.646 (95% CI: 0.33; 1.27) in dengue non-immune subjects. Additionally, the VE during Active Phase seemed to be highest in Malaysia (79.0%) compared to other four countries where VEs varied between 51% to 54% approximately. While the current study is not designed to address VE differentials, the brief descriptive statistics suggest that the VEs, overall, varied by vaccinees' age, baseline dengue serostatus and countries.

Table 4: VE against VCD due to any serotype, according to subject's age, baseline Dengue status and countries, Active Phase.

Age

Active Phase	(N)	CYD Gr Cases (n)	CYD Gr Person-years at risk	CYD Gr Incidence Density (95% CI)	Control Gr Cases (n)	Control Gr Person-years at risk	Control Gr Incidence Density (95% CI)	Vaccine efficacy % (95% CI)
2 to 5 years	(2483)	120	3219	3.7 (3.1; 4.4)	89	1584	5.6 (4.5; 6.9)	33.6 (11.7, 50.0)
6 to 8 years	(2820)	76	3726	2.0 (1.6;2.6)	85	1815	4.7 (3.7; 5.8)	56.5 (39.9, 68.5)
9 to 14 years	(4972)	90	6625	1.4 (1.1;1.7)	136	3224	4.2 (3.5; 5.0)	67.8 (57.6, 75.6)

Source: Reviewer's analysis. Note: The Applicant used age classifications 2-5, 6-11 and 12-14 years that may change in labels.

Baseline dengue status (Immunogenicity subset)

Active Phase	(N)	CYD Gr Cases (n)	CYD Gr Person-years at risk	CYD Gr Incidence Density % (95% CI)	Control Gr Cases (n)	Control Gr Person-years at risk	Control Gr Incidence Density (95% CI)	Relative Risk (95% CI)
Immune*	(1340)	18	1811	1.0 (0.6; 1.6)	34	880	3.9 (2.7; 5.4)	0.257 (0.14; 0.47)
Non-immune**	(643)	23	838	2.7 (1.7; 4.1)	18	423	4.3 (2.5; 6.6)	0.646 (0.33; 1.27)

*Dengue-immune subjects at baseline are defined as subjects with titers ≥ 10 (l/dil) against at least one dengue serotype at baseline. **Dengue non-immune subjects at baseline are defined as subjects with titers < 10 (l/dil) against all 4 serotypes at baseline. Source: Adapted from CSR CYD14, page 57 of 1568

Country

Active Phase	(N)	CYD Gr Cases (n)	CYD Gr Person-years at risk	CYD Gr Incidence Density (95% CI)	Control Gr Cases (n)	Control Gr Person-years at risk	Control Gr Incidence Density (95% CI)	Vaccine efficacy % (95% CI)
Indonesia	(1870)	40	2431	1.6 (1.2; 2.2)	43	1195	3.6 (2.6; 4.8)	54.3 (28.0; 71.0)
Malaysia	(1401)	9	1861	0.5 (0.2; 0.9)	21	910	2.3 (1.4; 3.5)	79.0 (52.3; 91.5)
Philippines	(3501)	143	4618	3.1 (2.6; 3.6)	150	2232	6.7 (5.7; 7.8)	53.9 (41.7; 63.6)
Thailand	(1170)	44	1529	2.9 (2.1; 3.8)	45	753	6.0 (4.4; 7.9)	51.8 (25.3; 68.9)
Vietnam	(2333)	50	3132	1.6 (1.2; 2.1)	50	1532	3.3 (2.4; 4.3)	51.1 (26.1; 67.6)

Source: Adapted from CSR CYD14, page 57 of 1568

6.1.10.2 Efficacy Conclusions

The overall VE against VCD post-dose 3 due to any serotype and regardless of severity was estimated as 56.5% (95% CI: 43.8; 66.4). The estimate's confidence lower bound exceeded the pre-specified limit of 25%, meeting the success criterion for primary objective.

The overall VE for post-dose 3 was consistent with the VE estimate of 54.8% (95% CI: 46.8; 61.7) for the Active Phase period (Table 3).

From the descriptive analysis by serotype (Table 3), the confidence lower bound for VE against VCD of serotype 2 was -9.2% during the post-dose 3 period and 10.4% during the Active Phase. The results showing confidence lower bounds considerably lower than the 25% limit are suggestive of relatively lower efficacy of the vaccine against VCD of serotype 2. From the descriptive analyses, overall, the VE against VCD of serotype 2 seemed to be the lowest of all serotypes.

Descriptive analyses also showed

- 67% reduction of hospitalized VCD cases during Active Phase.
- increased risk of VCD among children aged 2-5 years compared to the older groups and among those who were dengue non-immune at baseline.
- Malaysia had the highest level of overall VE of 79% when VEs for other countries ranged within 51% - 54% approximately.
- 80% reduction of VCD cases that meet WHO criterion.

6.1.11 Immunogenicity Analyses (secondary endpoints)

6.1.11.1 Analyses Results

Immunogenicity Level and Persistence

Neutralizing Ab level against each of the 4 dengue serotypes of CYD dengue vaccine constructs were measured at baseline, after Dose 2, after Dose 3, and 1, 2, 3, 4 and 5 years after Dose 3. The GMTs (Table 5) and percentage of subjects seropositive (titers ≥10(1/dil)) (Table 6) are presented by timepoints and serotypes. It appears that the GMTs among CYD vaccinees had a sharp rise from pre-injection to post-injection 3, declined over the following year, and afterward had further decline slowly, however. To illustrate, taking serotype 1 for example, the GMT at pre-injection 1 was 38.3, rose to 166 at post-injection 3, and after a year declined to 105, and to 98.5 in further long-term follow-up. Overall, the pattern holds for all serotypes. Despite decline, among vaccinees, high seropositive rates persisted longterm and at the end of follow-up the rates ranged from 79.2% to 89.6% across serotypes (Table 6).

Table 5: GMT by Serotype, Full Analysis Set for Immunogenicity

Serotype (PRNT- [l/dil])	Timepoint	CYD Dengue Vaccine Group			Control Group		
		M	GMT	(95% CI)	M	GMT	(95% CI)
Serotype 1	Pre-Inj 1	1309	38.3	(33.8; 43.5)	655	42.1	(35.0; 50.6)
	Post- Inj 2	1317	153	(137; 170)	654	46.1	(38.2; 55.7)
	Post- Inj 3	1316	166	(150; 183)	657	46.6	(38.7; 56.1)
	Year 1 FU Post-Inj 3	1290	105	(92.8; 119)	634	57.2	(46.9; 69.8)
	Year 2 FU Post-Inj 3	1286	90.1	(79.6; 102)	649	62.4	(51.5; 75.6)
	Year 3 FU Post-Inj 3	1294	104	(92.2; 118)	649	80.3	(66.0; 97.6)
	Year 4 FU Post-Inj 3	1286	98.5	(87.7; 111)	644	80.9	(66.9; 97.8)
Serotype 2	Pre-Inj 1	1313	55.3	(48.7; 62.9)	654	62.1	(51.7; 74.7)
	Post- Inj 2	1316	360	(329; 394)	655	69.5	(57.7; 83.6)
	Post- Inj 3	1314	355	(327; 386)	657	68.5	(57.1; 82.2)
	Year 1 FU Post-Inj 3	1298	194	(175; 214)	640	78.1	(64.8; 94.0)
	Year 2 FU Post-Inj 3	1284	150	(135; 166)	649	77.9	(65.3; 92.8)
	Year 3 FU Post-Inj 3	1295	217	(195; 241)	649	118	(97.9; 142)
	Year 4 FU Post-Inj 3	1285	168	(151; 187)	645	113	(94.7; 135)
Serotype 3	Pre-Inj 1	1307	40.1	(35.6; 45.1)	650	40.7	(34.5; 48.0)
	Post- Inj 2	1313	203	(184; 223)	656	40.8	(34.6; 48.1)
	Post- Inj 3	1314	207	(189; 226)	657	42.5	(36.2; 49.9)
	Year 1 FU Post-Inj 3	1298	186	(168; 206)	639	62.1	(51.8; 74.6)
	Year 2 FU Post-Inj 3	1255	118	(106; 132)	637	55.8	(47.1; 66.1)
	Year 3 FU Post-Inj 3	1294	158	(141; 177)	649	86.1	(71.9; 103)
	Year 4 FU Post-Inj 3	1286	153	(138; 170)	645	87.0	(73.1; 103)
Serotype 4	Pre-Inj 1	1313	25.3	(22.9; 28.0)	653	26.2	(22.6; 30.3)
	Post- Inj 2	1318	151	(139; 163)	655	24.4	(21.3; 28.1)
	Post- Inj 3	1315	151	(141; 162)	657	26.0	(22.6; 29.8)
	Year 1 FU Post-Inj 3	1293	85.5	(78.5; 93.0)	621	26.0	(22.4; 30.3)
	Year 2 FU Post-Inj 3	1268	70.0	(64.1; 76.4)	640	30.4	(26.2; 35.2)
	Year 3 FU Post-Inj 3	1293	97.5	(89.4; 106)	645	48.2	(41.4; 56.2)
	Year 4 FU Post-Inj 3	1286	89.5	(82.3; 97.3)	643	46.7	(40.2; 54.1)

M: number of subjects with available data for the relevant endpoint.
Source: CSR CYD14, page 60 of 1568

Table 6: Number and percentage of subjects PRNT titer>= 10 (1/dil) against each serotype with the parental dengue virus strains - Full Analysis Set for Immunogenicity

Serotype (PRNT-[1/dil])	Timepoint	CYD Dengue Vaccine Group			Control Group		
		n/M	(N=1323) %	(95% CI)	n/M	(N=660) %	(95% CI)
Serotype 1	**Pre-Inj 1 (V01)**	681/1309	52.0	(49.3; 54.8)	336/655	51.3	(47.4; 55.2)
	Post- Inj 2 (V04)	1171/1317	88.9	(87.1; 90.6)	356/654	54.4	(50.5; 58.3)
	Post- Inj 3 (V06)	1237/1316	94.0	(92.6; 95.2)	364/657	55.4	(51.5; 59.2)
	1-Year Follow-Up Post-Inj 3 (V07)	1030/1290	79.8	(77.6; 82.0)	353/634	55.7	(51.7; 59.6)
	2-Year Follow-Up Post-Inj 3 (V09)	961/1286	74.7	(72.3; 77.1)	379/649	58.4	(54.5; 62.2)
	3-Year Follow-Up Post-Inj 3 (V10)	1013/1294	78.3	(75.9; 80.5)	406/649	62.6	(58.7; 66.3)
	4-Year Follow-Up Post-Inj 3 (V11)	1018/1286	79.2	(76.8; 81.4)	420/644	65.2	(61.4; 68.9)
Serotype 2	**Pre-Inj 1 (V01)**	762/1313	58.0	(55.3; 60.7)	388/654	59.3	(55.5; 63.1)
	Post- Inj 2 (V04)	1281/1316	97.3	(96.3; 98.1)	409/655	62.4	(58.6; 66.2)
	Post- Inj 3 (V06)	1297/1314	98.7	(97.9; 99.2)	406/657	61.8	(58.0; 65.5)
	1-Year Follow-Up Post-Inj 3 (V07)	1194/1298	92.0	(90.4; 93.4)	421/640	65.8	(62.0; 69.5)
	2-Year Follow-Up Post-Inj 3 (V09)	1132/1284	88.2	(86.3; 89.9)	437/649	67.3	(63.6; 70.9)
	3-Year Follow-Up Post-Inj 3 (V10)	1170/1295	90.3	(88.6; 91.9)	463/649	71.3	(67.7; 74.8)
	4-Year Follow-Up Post-Inj 3 (V11)	1118/1285	87.0	(85.0; 88.8)	473/645	73.3	(69.7; 76.7)
Serotype 3	**Pre-Inj 1 (V01)**	743/1307	56.8	(54.1; 59.6)	386/650	59.4	(55.5; 63.2)
	Post- Inj 2 (V04)	1256/1313	95.7	(94.4; 96.7)	395/656	60.2	(56.4; 64.0)
	Post- Inj 3 (V06)	1274/1314	97.0	(95.9; 97.8)	401/657	61.0	(57.2; 64.8)
	1-Year Follow-Up Post-Inj 3 (V07)	1215/1298	93.6	(92.1; 94.9)	400/639	62.6	(58.7; 66.4)
	2-Year Follow-Up Post-Inj 3 (V09)	1098/1255	87.5	(85.5; 89.3)	411/637	64.5	(60.7; 68.2)
	3-Year Follow-Up Post-Inj 3 (V10)	1124/1294	86.9	(84.9; 88.7)	455/649	70.1	(66.4; 73.6)
	4-Year Follow-Up Post-Inj 3 (V11)	1152/1286	89.6	(87.8; 91.2)	470/645	72.9	(69.3; 76.3)
Serotype 4	**Pre-Inj 1 (V01)**	678/1313	51.6	(48.9; 54.4)	331/653	50.7	(46.8; 54.6)
	Post- Inj 2 (V04)	1253/1318	95.1	(93.8; 96.2)	339/655	51.8	(47.9; 55.6)
	Post- Inj 3 (V06)	1275/1315	97.0	(95.9; 97.8)	354/657	53.9	(50.0; 57.7)
	1-Year Follow-Up Post-Inj 3 (V07)	1156/1293	89.4	(87.6; 91.0)	314/621	50.6	(46.6; 54.6)
	2-Year Follow-Up Post-Inj 3 (V09)	1054/1268	83.1	(80.9; 85.1)	349/640	54.5	(50.6; 58.4)
	3-Year Follow-Up Post-Inj 3 (V10)	1154/1293	89.2	(87.4; 90.9)	423/645	65.6	(61.8; 69.2)
	4-Year Follow-Up Post-Inj 3 (V11)	1144/1286	89.0	(87.1; 90.6)	435/643	67.7	(63.9; 71.3)

N: number of subjects in the FASI. From V07 to V12, the analysis will be performed on Full Analysis set for Antibody persistence.
n: number of subjects experiencing the endpoint listed in the specified category.
M: number of subjects with available data for the relevant endpoint
Percentages and 95% CI are calculated according to the subjects with available data for the endpoint
Source: Adapted from CSR CYD14, Table 10.160, page 934-935.

Immunogenicity, Baseline Dengue Immune Status and Age

Table 7 illustrates that among CYD dengue vaccinees, GMT PD3, overall, was higher among the baseline immune subjects compared to those who were baseline non-immune, for each serotype. Similar result, as will be seen later (Table 13), was observed in pivotal study CYD15 as well. Additionally, from descriptive results, both baseline GMT and PD3 GMT increased with age for each serotype (Figure 4, Section 7.2).

Table 7: Geometric means Pre-dose 1 and Post-dose 3 for each serotype by dengue immune status at baseline in CYD Dengue Vaccine Group, CYD14 – full analysis set for immunogenicity

		Dengue Serotype 1		Dengue Serotype 2		Dengue Serotype 3		Dengue Serotype 4	
Study	Dengue immune status at baseline	Pre-dose 1 GMT (M) (95% CI)	Post-dose 3 GMT (M) (95% CI)	Pre-dose 1 GMT (M) (95% CI)	Post-dose 3 GMT (M) (95% CI)	Pre-dose 1 GMT (M) (95% CI)	Post-dose 3 GMT (M) (95% CI)	Pre-dose 1 GMT (M) (95% CI)	Post-dose 3 GMT (M) (95% CI)
CYD14	Non-immune	5.00 (419)	47.2 (418)	5.00 (419)	137 (417)	5.00 (419)	72.9 (417)	5.00 (419)	77.9 (418)
		(--)	(41.3; 53.9)	(--)	(121; 156)	(--)	(64.9;82.0	(--)	(69.6; 87.2)
	Immune	101 (888)	300 (890)	172 (892)	556 (889)	107 (887)	339 (889)	54.6 (891)	206 (889)
		(86.9;117)	(267; 338)	(151; 197)	(507; 610)	(93.9; 123)	(305; 376)	(48.7; 61.3)	(189; 223)

M: number of subjects with available Ab titer for the relevant endpoint
Immune subjects are subjects with titers ≥ LLOQ (1/dil) against at least one dengue serotype at baseline
Subjects with undetermined dengue immune status at baseline are included in the 'All' category
Source: Adapted from Summary of Clinical Efficacy, Table 10, page 114 of 358.

6.1.11.2 Immunogenicity Conclusions

1. The GMTs in CYD dengue vaccinees displayed sharp increase from pre-injection-1 to post-injection 2 and further to post-injection 3 for all 4 serotypes, but declined in first year post-dose 3 and in subsequent years, and retained at the end of 4 years post-injection 3. The seropositive rates after 4 years post dose 3 ranged between 79.2% and 89.6% for all serotypes. It's deferred to the clinical reviewer on the clinical significance of the observed level of seropositive persistence in comparison to the Control group where the seropositive rates ran at lower levels (than CYD dengue vaccinees') but showed tendency for slow increase from baseline and during four years post-injection 3 (Table 6), for all serotypes.

2. Post-dose 3 GMT was influenced by baseline dengue immune status for all serotypes (Table 7). The increase of baseline GMT with age will cause post-dose 3 GMT to increase with age as well. The conforming pattern is described in Figure 4 in Section 7.2.

6.2 Pivotal Study #2: Protocol CYD15

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

6.2.1 Objectives

Primary Objective:

To assess the efficacy of CYD dengue vaccine after 3 vaccinations at 0, 6 and 12 months in preventing symptomatic virologically-confirmed dengue cases, regardless of the severity, due to any of the four serotypes in children and adolescents aged 9 through 16 years at the time of inclusion.

Primary Endpoint
Symptomatic virologically-confirmed dengue cases occurring > 28 days after Dose 3 (during the Active Phase) and defined as:

- Acute febrile illness (i.e., temperature ≥ 38°C on at least 2 consecutive days)
- Virologically-confirmed by dengue RT-PCR and/or dengue NS1 ELISA Ag test

Statistical Methods for the primary objective
The statistical methodology was based on the use of the two-sided 95% confidence interval (CI) of the vaccine efficacy (VE). The methods were previously detailed in section 6.1.8 for pivotal study CYD14.

Secondary Objectives (selected):

Efficacy during Active Phase

To describe the efficacy of CYD dengue vaccine in preventing symptomatic virologically-confirmed dengue cases after the third dose to the end of the Active Phase:

- due to each of the 4 serotypes.

Immunogenicity Subset **(N=2000)**

To describe the Ab response to each dengue serotype after Dose 2, after Dose 3, and 1, 2, 3, 4 and 5 years after Dose 3.

Safety Objective:
Deferred to Safety Review by Dr. Huang.

6.2.2 Design Overview

The study design remained the same as was used in pivotal study CYD14 and described in 6.1.2 and Figure 1.

Countries or region included: Brazil, Colombia, Honduras, Mexico, Puerto Rico.
N=20,869 healthy subjects aged 9-16 years, randomized in 2:1 to the CYD vaccine group and placebo (NaCl 0.9%) control, respectively.
Immunogenicity subset=2000 subjects, 1333 in CYD dengue group and 667 in Control group.

6.2.3 Population

Healthy Subjects, 9–16 years old.
Randomized: 20,869
CYD dengue vaccination: 13,920
Placebo: 6,949

For inclusion and exclusion criteria, please refer to Clinical Reviewer report.

6.2.4 Sites and Centers

Study CYD15 was conducted in Brazil, Colombia, Honduras, Mexico and Puerto Rico.

6.2.5 Surveillance/Monitoring

Deferred to clinical reviewer's review.

6.2.7 Endpoints and Criteria for Study Success

Please refer to section 6.1.1 for the primary and secondary endpoints.

With the primary objective being to assess the efficacy of the CYD dengue vaccine (VE) after 3 injections in preventing the occurrence of symptomatic VCD cases of any serotype, the statistical methodology (ref. section 6.1.8) required that, for study success, the 2-sided 95% CI lower bound for VE exceed the pre-specified limit of 25%.

6.2.8 Statistical Considerations and Statistical Analysis Plan

Same as described in 6.1.8.

Analysis Populations
Same as for Study CYD14.

Titer measurements
Same as for Study CYD14.

Two key periods for VE calculation
Post-Dose 3: from 28 days post-dose 3 to the end of the Active Phase (**primary endpoint**).
Active Phase: from Day 0 (D0) to the end of the Active Phase.
(ref. SAP, Page 20 of 70）

6.2.9 Study Population and Disposition

Demographic characteristics at baseline
A total of 20,869 healthy subjects aged 9-16 years were randomized at a 2:1 ratio to either the CYD dengue vaccine group (N=13920) or the Control group (N=6949). The distribution by country of the randomized subjects was the following: Brazil 3548, Colombia 9743, Honduras 2799, Mexico 3464, and Puerto Rico 1315. A total of 2000 subjects (1334 in CYD group, 666 in Control group) were randomized in the immunogenicity subset. Females comprised 50% of the subjects, children aged 9-11 years were 46% and adolescents aged 12-16 years were 54%, and by ethnicity 99% or more subjects were Hispanic/Latino. In the immunogenicity subset, dengue seropositivity at baseline was 80.7% in the CYD vaccine group and 77.0% in the Control group (CSR CYD15, pages 186,188).

Disposition
Among the 20,869 randomized subjects, 20,856 received the first injection, 20,268 received the second injection and 19,938 received the third injection, regardless of the treatment groups. A total of 19,921 subjects completed the Active Phase period (95.5%), i.e. 13 months after the third injection. A total of 16,834 subjects completed the Year 3 Hospital Phase. Additionally, 18,834 subjects comprised per-protocol efficacy analysis set receiving 3rd dose, with 12573 subjects in

dengue vaccine group and 6261 subjects in control group. Overall, the subjects in both study groups showed high rate of compliance (>95%) and similar dispositions during trial, maintaining the dengue vaccine vs. control ratio of subjects at around 2:1 as planned for randomization. While further details appear in Appendix 1, concern for imbalance in subject disposition during trial was not discerned.

6.2.10 Efficacy Analyses

6.2.10.1 Analyses Results

Primary Objective

VE against VCD due to any serotype and severity. The study reported in the Active Phase a total of 10,053 febrile episodes, of which 670 were the virologically-confirmed episodes. A total of 662 subjects (i.e., cases) had at least one of these VCD episodes with any serotype, with 277 being in the CYD vaccine group and 385 in the Control group. For the post-dose 3 period (PD3) within Active Phase, the total symptomatic VCD cases reported were 397 with 176 in the CYD vaccine group and 221 in the Control group.

The VCD cases post-dose3 due to any serotype and severity are presented in Table 8 (primary endpoint analysis with a total of 397 cases per PPSE). The VCD cases (CYD vs Control group) due to any serotype and for each serotype, post-dose 3 and during Active Phase, are presented in Table 9. From Table 8, the overall primary estimate of vaccine efficacy PD3 due to any serotype and severity was 60.8% (95%CI: 52.0; 68.0). The 2-sided 95% CI lower bound was 52.0%, which exceeded the pre-specified VE limit of 25%, thus meeting the success criterion.

Table 8: Vaccine efficacy against symptomatic virologically-confirmed dengue post-dose 3 due to any of the 4 serotypes - Per Protocol Analysis Set for Efficacy

	CYD Dengue Vaccine Group (N=12574)				Control Group (N=6261)				Vaccine Efficacy	
	Cases	Person-years at risk	Density incidence (95% CI)	n Episodes	Cases	Person-years at risk	Density incidence (95% CI)	n Episodes	%	(95% CI)
Symptomatic VCD	176	11792	1.5 (1.3;1.7)	176	221	5809	3.8 (3.3;4.3)	221	60.8	(52.0; 68.0)

Cases: number of subjects with at least one symptomatic virologically-confirmed dengue episode from 28 days post-injection 3 to the end of Active Phase.
Density incidence: data are cases per 100 person-years at risk. The person-years at risk are the cumulative time (in years) until the participant was diagnosed with VCD or until the end of the active period, whichever came first. The person-years at risk presented in the tables are the sum of individual units of time for which the participants contributed to the analyses. Incidence density was calculated as the number of cases divided by the cumulative person-years at risk n Episodes: number of virologically-confirmed dengue episodes in the considered period.
Source: Adapted from CSR CYD15, Table 5.1, page 194 of 1622.

Secondary Objectives

1. VE by Serotype. The post-dose3 VE of 60.8% (95%CI: 52.0; 68.0) results as above was consistent with post-dose3 VE of 61.3% (95%CI: 52.8; 68.2) from mFASE population (Table 9). From serotype-specific descriptive analyses, the post-dose3 VE estimates ranged from 42.3% to 77.7%. The confidence LB of 14.0% for serotype 2 indicates limited efficacy performance, post-dose 3. For Active Phase, the VE for serotype 2 was lowest at about 50% but the confidence LB 31.8% was above the 25% limit.

Table 9: VE against VCD due to any and each serotype, post-Dose 3 and during Active Phase.

	Post-Dose 3	Post-Dose 3	Active Phase	Active Phase
	# cases CYD vaccn vs Control	VE (%) (95% CI)	# cases CYD vaccn vs Control	VE (%) (95% CI)
Any serotype	185/236	61.3 (52.8; 68.2)	277/385	64.7 (58.7; 69.8)
Serotype1	66/66	50.3 (29.1; 65.2)	99/109	54.8 (40.2; 65.9
Serotype2	58/50	42.3 (14.0; 61.1)	84/84	50.2 (31.8; 63.6)
Serotype3	43/82	74.0 (61.9, 82.4)	55/106	74.2 (63.9; 81.7)
Serotype4	18/40	77.7 (60.2; 88.0)	32/83	80.9 (70.9; 87.7)

Cases: number of subjects with at least one symptomatic VCD episode in the considered period.
Dengue virus serotypes are determined by Simplexa RT-PCR.
Subjects with a virologically-confirmed dengue of the studied serotype between V01 and 28 days after injection 3 are excluded from the corresponding serotype-specific analysis.
Post-Dose 3: period from 28 days post-Dose 3 to the end of the Active Phase (mFASE)
Active Phase: period from Day 0 to the end of the Active Phase (FASE)
Unserotyped cases (PD3: 6 in CYD and 3 in Control; Active Phase: 15 in CYD and 16 in Control) had incidence rate as low as ≤0.1, involved uncertainty for precise clinical interpretation, were not considered in clinical labelling and as such not included in serotype analysis.
Source: Adapted from CSR CYD15, Table 5.2, Table 5.4 and Table 5.5, page 196, 200 and 204, respectively.

2. Hospitalization with VCD cases

Active Phase reported a total of 60 subjects hospitalized as VCD cases, with 17 in the CYD dengue group and 43 in the Control group, with any serotype. Overall, the CYD vaccine showed a risk-reduction of 80.3% (95% CI: 65.0; 89.0) in the incidence of hospitalized VCD cases compared to Control (CSR CYD15, page 56).

Post-Dose 3. During this period, 40 subjects (12 in CYD dengue vaccine and 20 in Control) with VCD due to any serotype were hospitalized (CSR CYD15, Table 5.27, page 254 of 1622). The submission reported a risk-reduction of 78.6% (95% CI: 57.0; 90.0) in the incidence of hospitalized VCD cases in the CYD vaccine group vs Control group (CSR CYD15, page 56).

3. WHO Criteria and VCD Cases

Post-dose 3, 6 subjects reported VCD episodes (due to any serotype) that met WHO criteria. During Active Phase, such subjects were 11. Overall, the VEs were 90.0% (95% CI: 10.7; 99.8) and 95.0% (95% CI: 64.9; 99.9) for the two periods, respectively (CSR CYD15, page 56).

4. VE and Covariates

Age. The observed VE against VCD due to any serotypes in the Active Phase was 61.7% (95% CI: 52.3; 69.3) in the age group 9 to 11 years, and 67.6% (95% CI: 59.3; 74.3) in 12 to 16 years. It appears that VEs might not have marked increase with age in the older age groups of children (CSR CYD15, Table 5.19, page 230 of 1622). The VEs for post-dose 3 had similar trend and are not included in the review.

Baseline dengue immune status and country. Considering the immunogenicity subset only, from Table 10, the immune subjects displayed a VCD relative risk of 0.163 (95% CI: 0.06; 0.38) versus 0.568 (0.20; 1.62) in non-immune subjects, during the Active Phase. In post-dose 3, the relative-risk values did not largely change and as such are not presented in the review.

Country. The VE was evaluated for each country. Again, from Table 10 lower panel, the observed VEs during the Active Phase seemed to be lower in Mexico [31.3% (95% CI:1.3; 51.9)] and Puerto Rico [57.6% (95% CI: -2.5; 82.8)], compared to other countries. For the post-dose 3 period, the VEs in other countries did not markedly change from the Active Phase and as

such are not included in the review, but did reduce to 8.8% (95% CI: -50.3; 43.5) and 43.4% (95% CI: -68.5; 80.6), respectively, in Mexico and Puerto Rico. The uncertainty of the VE estimate for Puerto Rico is large due to small sample size and low incidence rate.

Overall, the VEs varied by baseline dengue immune status and as well in countries.

Table 10**:** Incidence of symptomatic VCD cases due to any serotype during the Active Phase, by baseline dengue status and Country

Baseline dengue status (Immunogenicity Subset)

Active Phase	**CYD Gr Cases (n)**	**CYD Gr Person-years at risk**	**CYD Gr Incidence Density % (95% CI)**	**Control Gr Cases (n)**	**Control Gr Person-years at risk**	**Control Gr Incidence Density (95% CI)**	**Relative Risk (95% CI)**
Immune*	8	2116	0.4 (0.2; 0.7)	23	994	2.3 (1.5;3.5)	0.163 (0.06; 0.38)
Non-immune**	9	500	1.8 (0.8; 3.4)	9	284	3.2 (1.5; 5.9)	0.568 (0.20; 1.62)

*Baseline dengue-immune (dengue-seropositive) subjects are defined as subjects with titers >= 10 (1/dil) against at least one dengue serotype at baseline. **Baseline dengue-non-immune (dengue-seronegative) subjects are defined as subjects with titers < 10 (1/dil) against any of the four dengue serotypes at baseline.
Source: Adapted from CSR CYD15, Table 5.23, page 238 of 1622.

Country

Active Phase (FASE)	**(N)**	**CYD Gr Cases (n)**	**CYD Gr Person-years at risk**	**CYD Gr Incidence Density (95% CI)**	**Control Gr Cases (n)**	**Control Gr Person-years at risk**	**Control Gr Incidence Density (95% CI)**	**Vaccine efficacy % (95% CI)**
Brazil	(3548)	38	4588	0.8 (0.6; 1.1)	81	2200	3.7 (2.9; 4.6)	77.5 (66.5; 85.1)
Colombia	(9743)	108	12497	0.9 (0.7; 1.0)	164	6172	2.7 (2.3; 3.1)	67.5 (58.3;74.7)
Hondurus	(2799)	42	3607	1.2 (0.8; 1.6)	71	1765	4.0 (3.2; 5.0)	71.1 (57.0; 80.7)
Mexico	(3464)	78	4522	1.7 (1.4; 2.1)	56	2231	2.5 (1.9; 3.2)	31.3 (1.3; 51.9)
Puerto Rico	(1315)	11	1669	0.7 (0.3; 1.2)	13	836	1.6 (0.8; 2.6)	57.6 (-2.5; 82.8)

N=20869 (with 13920 for CYD Gr, and 6949 for Control Gr. (CSR CYD15, page 52-53 of 1622)
Cases: number of subjects with at least one symptomatic virologically-confirmed dengue episode during the Active Phase.
Density incidence: data are cases per 100 person-years at risk.
Source: Adapted from CSR CYD15, Table 5.20, page 232 of 1622.

6.2.10.2 Efficacy Conclusions

The study's primary efficacy objective was met. The overall VE against VCD post-dose 3 due to any serotype and regardless of severity was 60.8% (95% CI: 52.0; 68.0), with confidence lower bound exceeding the pre-specified limit of 25% (Table 8).

The overall VE for post-dose 3 was consistent with VE estimate of 64.7% (95% CI: 58.7; 69.8) for the Active Phase period (Table 9).

From descriptive analysis by serotype (Table 9), the VE against VCD of serotype 2 appeared lowest during the post-dose 3 and Active Phase periods. The LB post-dose 3 fell below 25%.

Descriptive analyses also showed

- 80.3% (95% CI: 65.0; 89.0) reduction in the incidence of hospitalized VCD cases during Active Phase.
- VEs might not have marked increase in the older age-group of children, both in the post-dose 3 and Active Phase periods (ref. *VE and Covariates* under *Secondary Objectives*).

- the baseline dengue immune subjects displayed higher VE compared to the baseline dengue non-immune subjects, in both post-dose 3 and Active Phase periods.
- VE varied by countries, Mexico and Puerto Rico had lower VE estimates than other countries.
- 90% or more reduction in an individual's risk of having VCDs that meet WHO criteria.

6.2.11 Immunogenicity Analyses (secondary endpoints)

6.2.11.1 Analyses Results

Immunogenicity Level and Persistence

Neutralizing Ab level against each of the 4 dengue serotypes of CYD dengue vaccine constructs were measured at baseline, after Dose 2, after Dose 3, and 1, 2, 3, 4 and 5 years after Dose 3. Table 11 and Table 12, respectively, present GMTs and percentage of subjects seropositive

Table 11**:** Summary of GMTs of dengue antibodies against each serotype with the parental dengue virus strains – Full Analysis Set for Immunogenicity

Serotype (PRNT-[[1/dil])	**Timepoint**	**CYD Dengue Vaccine Group (N=1301)**			**Control Group (N=643)**		
		M	GMT	(95% CI)	M	GMT	(95% CI)
Serotype 1	**Pre-Inj 1 (V01)**	1297	128	(112; 145)	641	119	(98.7; 142)
	Post- Inj 2 (V04)	1296	458	(406; 517)	638	128	(106; 154)
	Post- Inj 3 (V06)	1291	395	(353; 441)	640	121	(101; 145)
	1-Year Follow-Up Post-Inj 3 (V07)	1261	266	(234; 302)	629	146	(121; 176)
	2-Year Follow-Up Post-Inj 3 (V09)	1222	209	(185; 237)	612	142	(118; 171)
	3-Year Follow-Up Post-Inj 3 (V10)	1177	259	(229; 293)	577	177	(147; 214)
	4-Year Follow-Up Post-Inj 3 (V11)	1069	397	(347; 455)	529	283	(227; 353)
Serotype 2	**Pre-Inj 1 (V01)**	1299	138	(123; 156)	640	115	(97.2; 136)
	Post- Inj 2 (V04)	1297	622	(566; 684)	639	124	(104; 148)
	Post- Inj 3 (V06)	1291	574	(528; 624)	640	129	(109; 152)
	1-Year Follow-Up Post-Inj 3 (V07)	1264	371	(336; 409)	629	145	(122; 173)
	2-Year Follow-Up Post-Inj 3 (V09)	1223	339	(307; 374)	612	173	(146; 206)
	3-Year Follow-Up Post-Inj 3 (V10)	1176	342	(311; 376)	577	187	(157; 222)
	4-Year Follow-Up Post-Inj 3 (V11)	1069	387	(346; 432)	528	241	(199; 292)
Serotype 3	**Pre-Inj 1 (V01)**	1300	121	(108; 136)	639	114	(95.9; 136)
	Post- Inj 2 (V04)	1297	556	(506; 610)	639	117	(98.3; 139)
	Post- Inj 3 (V06)	1291	508	(465; 555)	640	124	(105; 147)
	1-Year Follow-Up Post-Inj 3 (V07)	1265	292	(263; 325)	629	137	(114; 165)
	2-Year Follow-Up Post-Inj 3 (V09)	1219	303	(274; 334)	610	170	(142; 203)
	3-Year Follow-Up Post-Inj 3 (V10)	1175	326	(295; 362)	577	186	(156; 223)
	4-Year Follow-Up Post-Inj 3 (V11)	1069	371	(331; 416)	529	237	(193; 290)
Serotype 4	**Pre-Inj 1 (V01)**	1297	43.6	(39.6; 48.0)	640	39.0	(33.9; 44.7)
	Post- Inj 2 (V04)	1295	261	(242; 281)	637	40.9	(35.5; 47.0)
	Post- Inj 3 (V06)	1291	241	(226; 258)	640	44.3	(38.6; 50.8)
	1-Year Follow-Up Post-Inj 3 (V07)	1265	174	(161; 188)	625	51.5	(44.3; 59.8)
	2-Year Follow-Up Post-Inj 3 (V09)	1223	138	(128; 149)	612	56.5	(48.8; 65.5)
	3-Year Follow-Up Post-Inj 3 (V10)	1175	173	(160; 185)	577	76.5	(66.1; 88.6)
	4-Year Follow-Up Post-Inj 3 (V11)	1069	190	(173; 208)	529	101	(85.1; 119)

M: number of subjects available for the endpoint.
Source: Adapted from CSR CYD15, Table 6.3, page 304-305.

(≥10(1/dil)) at different time points of Ab measurements, for each serotype. As in CYD14, the GMTs among CYD dengue vaccinees rose from pre-injection 1 to post-injection 2 or 3, declined over the following year and mostly slowly afterward, but maintained Ab level above the baseline and Control level during follow-up. Additionally, both GMT and percent of subjects seropositive pre-injection 1 were comparable between the CYD vaccine group and Control group. Overall, the patterns hold for all serotypes. High seropositive rates (close to 90% or higher) for all serotypes persisted long-term among the CYD dengue vaccinees.

Table 12: Number and percentage of subjects with PRNT titer>= 10 (1/dil) against each serotype with the parental dengue virus strains - Full Analysis Set for Immunogenicity

Serotype (PRNT- [1/dil])	Timepoint	CYD Dengue Vaccine Group (N=1301)			Control Group (N=643)		
		n/M	%	(95% CI)	n/M	%	(95% CI)
Serotype 1	**Pre-Inj 1 (V01)**	944/1297	72.8	(70.3; 75.2)	452/641	70.5	(66.8; 74.0)
	Post- Inj 2 (V04)	1202/1296	92.7	(91.2; 94.1)	458/638	71.8	(68.1; 75.2)
	Post- Inj 3 (V06)	1225/1291	94.9	(93.5; 96.0)	475/640	74.2	(70.6; 77.6)
	1-Year Follow-Up Post-Inj 3 (V07)	1079/1261	85.6	(83.5; 87.5)	463/629	73.6	(70.0; 77.0)
	2-Year Follow-Up Post-Inj 3 (V09)	1026/1222	84.0	(81.8; 86.0)	464/612	75.8	(72.2; 79.2)
	3-Year Follow-Up Post-Inj 3 (V10)	1041/1177	88.4	(86.5; 90.2)	460/577	79.7	(76.2; 82.9)
	4-Year Follow-Up Post-Inj 3 (V11)	948/1069	88.7	(86.6; 90.5)	416/529	78.6	(74.9; 82.1)
Serotype 2	**Pre-Inj 1 (V01)**	988/1299	76.1	(73.6; 78.4)	472/640	73.8	(70.2; 77.1)
	Post- Inj 2 (V04)	1265/1297	97.5	(96.5; 98.3)	480/639	75.1	(71.6; 78.4)
	Post- Inj 3 (V06)	1272/1291	98.5	(97.7; 99.1)	494/640	77.2	(73.7; 80.4)
	1-Year Follow-Up Post-Inj 3 (V07)	1189/1264	94.1	(92.6; 95.3)	496/629	78.9	(75.5; 82.0)
	2-Year Follow-Up Post-Inj 3 (V09)	1147/1223	93.8	(92.3; 95.1)	498/612	81.4	(78.1; 84.4)
	3-Year Follow-Up Post-Inj 3 (V10)	1119/1176	95.2	(93.8; 96.3)	477/577	82.7	(79.3; 85.7)
	4-Year Follow-Up Post-Inj 3 (V11)	1000/1069	93.5	(91.9; 94.9)	434/528	82.2	(78.7; 85.4)
Serotype 3	**Pre-Inj 1 (V01)**	995/1300	76.5	(74.1; 78.8)	470/639	73.6	(70.0; 76.9)
	Post- Inj 2 (V04)	1278/1297	98.5	(97.7; 99.1)	484/639	75.7	(72.2; 79.0)
	Post- Inj 3 (V06)	1270/1291	98.4	(97.5; 99.0)	499/640	78.0	(74.6; 81.1)
	1-Year Follow-Up Post-Inj 3 (V07)	1173/1265	92.7	(91.2; 94.1)	479/629	76.2	(72.6; 79.4)
	2-Year Follow-Up Post-Inj 3 (V09)	1155/1219	94.7	(93.3; 95.9)	492/610	80.7	(77.3; 83.7)
	3-Year Follow-Up Post-Inj 3 (V10)	1113/1175	94.7	(93.3; 95.9)	474/577	82.1	(78.8; 85.2)
	4-Year Follow-Up Post-Inj 3 (V11)	996/1069	93.2	(91.5; 94.6)	433/529	81.9	(78.3; 85.0)
Serotype 4	**Pre-Inj 1 (V01)**	885/1297	68.2	(65.6; 70.8)	416/640	65.0	(61.2; 68.7)
	Post- Inj 2 (V04)	1255/1295	96.9	(95.8; 97.8)	427/637	67.0	(63.2; 70.7)
	Post- Inj 3 (V06)	1267/1291	98.1	(97.2; 98.8)	441/640	68.9	(65.2; 72.5)
	1-Year Follow-Up Post-Inj 3 (V07)	1200/1265	94.9	(93.5; 96.0)	431/625	69.0	(65.2; 72.6)
	2-Year Follow-Up Post-Inj 3 (V09)	1153/1223	94.3	(92.8; 95.5)	444/612	72.5	(68.8; 76.1)
	3-Year Follow-Up Post-Inj 3 (V10)	1140/1175	97.0	(95.9; 97.9)	453/577	78.5	(74.9; 81.8)
	4-Year Follow-Up Post-Inj 3 (V11)	1007/1069	94.2	(92.6; 95.5)	416/529	78.6	(74.9; 82.1)

n: number of subjects experiencing the endpoint listed in the specified category.
M: number of subjects with available data for the relevant endpoint.
Source: Adapted from CSR CYD15 Table 6.1, page 298 of 1622.

Immunogenicity, Baseline Dengue Immune Status, and Age

Table 13 illustrates that among CYD dengue vaccinees, PD3 GMT, overall, was higher among the baseline dengue immune subjects compared to those who were baseline dengue non-immune, for each serotype. The GMTs with baseline dengue non-immune status seem depressed. Similar result was seen in pivotal study CYD14 (Table 7) also. Additionally, from descriptive results, both baseline GMT and PD3 GMT increased with subject's age, for each serotype (Figure 4, Section 7.2).

Table 13: Geometric means Pre-dose 1 and Post-dose 3 for each serotype by dengue immune status at baseline in CYD Dengue Vaccine Group, CYD15 – full analysis set for immunogenicity

		Dengue Serotype 1		Dengue Serotype 2		Dengue Serotype 3		Dengue Serotype 4	
Study	**Dengue immune status at baseline**	**Pre-dose 1 GMT (M) (95% CI)**	**Post-dose 3 GMT (M) (95% CI)**	**Pre-dose 1 GMT (M) (95% CI)**	**Post-dose 3 GMT (M) (95% CI)**	**Pre-dose 1 GMT (M) (95% CI)**	**Post-dose 3 GMT (M) (95% CI)**	**Pre-dose 1 GMT (M) (95% CI)**	**Post-dose 3 GMT (M) (95% CI)**
CYD15	**Non-immune**	5.00 (251)	35.3 (249)	5.00 (251)	105 (249)	5.00 (251)	93.6 (249)	5.00 (251)	89.5 (249)
		(--)	(29.8; 41.9)	(--)	(89.3; 125)	(--)	(80.3; 109)	(--)	(76.1; 105)
	Immune	278 (1046)	703 (1040)	306 (1048)	860 (1040)	261 (1048)	762 (1040)	73.3 (1046)	306 (1040)
		(247; 313)	(634; 781)	(277; 338)	(796; 930)	(235; 289)	(699; 830)	(66.6; 80.7)	(286; 328)

M: number of subjects with available Ab titer for the relevant endpoint
Immune subjects are subjects with titers ≥ LLOQ (1/dil) against at least one dengue serotype at baseline
Subjects with undetermined dengue immune status at baseline are included in the 'All' category
Source: Adapted from Summary of Clinical Efficacy Table 10, page 114 of 358.

6.2.11.2 Immunogenicity Conclusions

1. The GMTs in CYD dengue vaccinees increased from pre-injection 1 level to post-injection 2 and to post-injection 3 for all 4 serotypes. During the first year post-dose 3 and in subsequent years, these GMTs declined, but maintained all along the higher level above baseline and Control level.

2. The proportion of subjects seropositive pre-injection-1 was comparable between the CYD dengue vaccine and Control groups. While the seropositive rates in Control group remained more or less stable and stayed between 70% and 82%, the rates post-injection 2 in CYD dengue vaccinees showed persistence to hold within the range from 84% to 98%. The patterns hold for all serotypes.

3. Post-dose 3 GMT was influenced by baseline dengue immune status, when showing higher values among the baseline dengue immune subjects in comparison to the baseline dengue non-immune subjects. Such influence coupled with increased exposure with age can make GMT to increase with age, a pattern shown in Figure 4, Section 7.2.

6.3 Supportive Studies

6.3.1 General Information

Studies CYD22, CYD28 and CYD47 were phase II supportive studies from endemic areas. The Applicant selected adults' (18-45 years age) immunogenicity data from these phase II studies for a descriptive immunogenicity bridging with younger vaccinees (2-16 years age) in pivotal studies CYD14 and CYD15 (Table 22). A detailed briefing about CYD22, CYD28 and CYD47 is provided in Table 14. Following Table 14, a brief description about CYD17 (phase III lot consistency but stated as supportive) and CYD23 (phase II supportive, but extended for safety follow-up which was coded as CYD57) is provided.

Table 14: Brief Description about CYD22, CYD28 and CYD47

Study	Objectives, design and schedules	Study Population and # subjects randomized	Disposition and Conclusions
CYD22 (Viet Nam. Endemic areas. 14 Mar 2009 to Aug 2014 (including 4years post injection 3 follow-up)	Title: *Immunogenicity and Safety of Tetravalent Dengue Vaccine in Healthy Subjects Aged 2 to 45 Years in Viet Nam.* Phase II, randomized, controlled, blind-observer, monocenter trial to describe: - dengue humoral immune response before and after each injection, - safety, after each injection, - 4 year post-injection 3 follow-up: antibody persistence and safety. - detection of symptomatic dengue cases. Randomized in two groups: Group 1: CYD dengue vaccine (~5 log10CCID50/serotype 1, 2, 3, 4) at D0, M6 and M12. Group 2: Meningococcal Polysaccharide A+C vaccine at D0. Placebo (NaCl 0.4% containing human serum albumin 2.5%) at M6. Typhoid Vi Polysaccharide vaccine (Typhim Vi®) at M12. 0.5 mL/injection. Subcutaneous injection.	Healthy Subjects, 2-45 years. Randomized: 180 Group 1: 120 20 adults (18-45 years) 20 adolescents (12-17 years) 40 children (6–11 years) 40 children (2–5 years) Group 2: 60 10 adults 10 adolescents 20 children (6–11 years) 20 children (2–5 years).	Disposition: 172 subjects received third injection regardless of treatment groups, 166 subjects completed 4-year follow-up. Conclusion: Observed satisfactory safety profile of CYD dengue vaccine. Seropositivity rate 92.1% against all 4 serotypes following injection 3. GMTs increased after injection 3, declined over time but remained above baseline 4 years after third injection.
CYD28 (Singapore, Endemic area, 07 Apr 2009 to 22 Oct 2014, (including 4 years post injection 3 follow- up))	*Title Immunogenicity and Large-Scale Safety of Tetravalent Dengue Vaccine in Healthy Subjects Aged 2 to 45 Years in Singapore.* Phase II, randomized, controlled, blind-observer (1st injection), single blind (2nd and 3rd injection), multicenter trial, with objectives aiming at - Descriptive safety after each injection. - Descriptive dengue humoral response before and after each injection in a subset of subjects. - Descriptive cellular immune response after the 2nd and 3rd injection in a subset of subjects. - 4-year post-injection 3 follow-up: antibody persistence (in a subset of subjects) and safety. - Detection of symptomatic hospitalized dengue cases. Randomized in 2 groups. Group 1: CYD dengue vaccine (~5 log10CCID50/serotype 1, 2, 3, 4) at D0, M6 and M12. Group 2: *If < 12 years* Placebo (NaCl 0.9%) at D0. Hepatitis A vaccine (Havrix®) at M6 and M12. *If ≥ 12 years* Placebo (NaCl 0.9%) at D0. Influenza vaccine (Vaxigrip®) at M6 and M12. 0.5 mL/injection. Subcutaneous injection for all but Hepatitis A vaccine: intramuscular injection.	Healthy Subjects, 2-45 years. Randomized: Randomized: 1198 Group 1: 898 521 adults 141 adolescents 236 children Group 2: 300 174 adults 46 adolescents 80 children	Disposition: 1118 subjects received third injection regardless of treatment groups, 1046 subjects completed 4-year follow-up. Observed satisfactory safety profile of CYD dengue vaccine. Seropositivity rate 66.7% against all 4 serotypes after CYD vaccine injection 3. GMTs increased after third injection but declined over time and remained above baseline 4 years after third injection.
CYD47 (India, Endemic area, 27 Mar 2012 to 07 Dec 2013)	Title: *Immunogenicity and Safety of a Tetravalent Dengue Vaccine in Healthy Adult Subjects Aged 18 to 45 Years in India* Phase II, randomized, placebo controlled, blind-observer, multicenter trial, with objectives to obtain - Descriptive dengue humoral immune response before the 1st injection and after each	Healthy subjects, 18-45 years. Randomized: 189 Group 1: 128 Group 2:61	Disposition: 172 subjects received third injection regardless of treatment groups. Observed satisfactory safety profile for CYD dengue vaccine, 97.4% the CYD

	injection. - Descriptive safety after each injection. - Detection of symptomatic dengue cases. - 6-month post-injection 3 safety follow-up. Randomized in 2 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 injection.		dengue vaccinees were seropositive against all 4 serotypes after third injection.

Source: (Adapted) Summary of Clinical Efficacy, pages 61-66, Table 1 (page 26-45).

6.3.2 CYD17

General Information:
This study was conducted in dengue non-endemic region (Australia) and contributed immunogenicity data for evaluating clinical consistency of three manufacturing lots. Although conducted as phase III (Table 1), the study was not a part of pivotal efficacy evaluation conducted in dengue endemic regions. The description below is confined to providing study's salient features, results and conclusions.

Title: Lot-to-Lot Consistency and Bridging Study of a Tetravalent Dengue Vaccine in Healthy Adults in Australia

Time period*:*
Date of first visit of the first subject: 05 October 2010
Date of last contact of the last subject (including the 6-month follow-up): 12 June 2012

Primary Objective:
To establish consistency of three manufacturing lots, which is to demonstrate that three different Phase III lots of CYD dengue vaccine induce an equivalent immune response in terms of post-Dose 3 geometric mean titers (GMTs) against the four parental serotypes.

Study Design
The primary endpoint is the neutralizing antibody (Ab) level against each of the four dengue virus serotypes measured 28 days post-dose 3 of the CYD dengue vaccine. The study was a multi-center, observer-blind, randomized, placebo-controlled, Phase III evaluation of 4 lots of CYD dengue vaccine based on 715 healthy adult subjects of age 18 to 60 years in Australia. Each subject received 3 doses at 6 months apart, with safety follow-up for 6 months. The planned number of subjects (N=715) were randomized in a 3:3:3:3:1 ratio to receive one of the 4 lots of CYD dengue vaccine (Phase III Lot 1, Phase III Lot 2, Phase III Lot 3, Phase II Lot) or placebo (NaCl 0.9%). Each subject provided blood samples at baseline and 28 days post-dose 3.

Statistical Methods
Equivalence among the three lots was demonstrated if for each pair of phase III lots the GMT ratio was contained between ½ and 2, for each serotype. That means, the lower limit of the 2-

sided 95% CI for the difference between two log10GMT's in lot-pairs must be > -0.301 and the upper limit <0.301, for each serotype, to establish lot consistency.

Results: A total of 715 subjects were randomized (164 subjects in Phase III Lot 1, 163 subjects in Phase III Lot 2, 163 subjects in Phase III Lot 3, 168 subjects in Phase II lot and 57 subjects in placebo group), and a total of 712 subjects were vaccinated at Visit 01 and 614 subjects completed the study up to 28 days after third injection. Table 15 describes GMTs for each lot and Table 16 provides pairwise differences in log10GMTs and 95% CIs.

Table 15**:** GMT of antibodies against parental dengue virus serotypes among three Phase III lots 28 days after the third injection - Per Protocol Analysis Set

	Phase III Lot 1 (N=129)			**Phase III Lot 2 (N=123)**			**Phase III Lot 3 (N=124)**			**Phase II Lot (N=128)**		
Components	**M**	**GMT**	**(95% CI)**	**M**	**GMT**	**(95% CI)**	**M**	**GMT**	**(95% CI)**	**M**	**GMT**	**(95% CI)**
Serotype 1	129	20.6	(16.9;25.1)	123	18.1	(14.8;22.2)	124	17.1	(13.9;21.2)	128	15.1	(12.4;18.4)
Serotype 2	129	65.9	(50.6;85.7)	123	44.1	(33.3;58.3)	124	58.1	(43.2;78.2)	128	25.7	(20.6;32)
Serotype 3	129	74.2	(60.1;91.7)	123	65	(53.2;79.3)	124	71.6	(58.2;88.2)	128	83.6	(71.1;98.4)
Serotype 4	129	131.8	(101.4;171.3)	123	94.6	(75.3;118.7)	124	108.5	(84.2;139.7)	127	115.4	(92.8;143.5)

M: Number of subjects available for the endpoint.
Source: Adapted from CSR CYD17, page 31, 110 of 995.

Table 16: Difference of log10GMT of antibodies against parental dengue virus serotypes among three Phase III lots 28 days after the third injection - Per Protocol Analysis Set

	Difference of $_{Log10}$ GMT					
	Lot 1 – Lot 2		**Lot 2 – Lot 3**		**Lot 3 – Lot 1**	
Components	**Diff**	**(95% CI)**	**Diff**	**(95% CI)**	**Diff**	**(95% CI)**
Serotype 1	0.055	(-0.067;0.178)	0.024	(-0.102;0.151)	-0.080	(-0.204;0.045)
Serotype 2	0.174	(0.009;0.340)	-0.120	(-0.297;0.056)	-0.054	(-0.225;0.117)
Serotype 3	0.058	(-0.068;0.184)	-0.042	(-0.167;0.082)	-0.016	(-0.144;0.113)
Serotype 4	0.144	(-0.006;0.295)	-0.060	(-0.207;0.088)	-0.085	(-0.242;0.073)

Note: Lot consistency for each pair of lots was demonstrated if for each pair of lots and each serotype, the lower limit of the 2-sided 95% CI was > -0.301 and the upper limit was < 0.301.
Source: CSR CYD17, page 30 of 995.

From the differences (and 95%CIs) of log10GMTs (Table 16) between lots in each lot-pair and for each serotype, lot consistency criteria were satisfied, except for serotype 2 Lot1-Lot2 where the observed upper limit of 0.340 exceeded 0.301, the pre-specified limit for lot consistency. The Applicant contended that "Only 1 statistical comparison out of 12 was not achieved but was considered as not clinically significant based on the similarity between Phase III lots for all serotypes, including serotype 2 and since the GMTs for serotype 2 observed in each Phase III lot (65.9 [1/dil], 44.1 [1/dil] and 58.1 [1/dil], respectively) were consistently higher than the GMT observed in the Phase II lot (25.7 [1/dil])" (CSR CYD17, page 31 of 995). Whether such contention entails safety concern is deferred to clinical decision making.

Conclusion
The statistical criteria for lot consistency were satisfied, except for one comparison, Lot 1-Lot 2 for serotype 2, where the observed confidence upper limit of 0.340 on log10GMTs difference exceeded 0.301, the pre-specified limit for lot consistency. The missing of one sole comparison out of 12 has been claimed in the submission as not clinically significant based on the immunogenicity profile of each lot, in comparison to a lot used in phase II development. Whether such claim involves concern for clinical rationale and safety is deferred for expert's decision making.

6.3.3 CYD23

***General Information*:**
This study was a proof of concept phase IIb, as such supportive, efficacy study conducted in 1 center in Thailand where dengue is endemic. Following the trial's Active Phase, which is from the start of the trial to 13 months after the third injection, the CYD23 subjects were included in long-term safety follow-up at the request of the local government. The description below briefs on study's salient features, results and conclusions. Additional details appeared in Table 1.

Title: Efficacy and Safety of Dengue Vaccine in Healthy Children Aged 4 to 11 Years in Thailand.

Primary Objective
To assess the efficacy of the CYD dengue vaccine after 3 injections in preventing the occurrence of symptomatic VCD cases.

Study Design
CYD23 was a randomized, observer-blind, controlled Phase IIb study conducted in 1 center in Thailand. A total of 4002 healthy children (4 to 11 years) were randomized into 2 groups: (1) 2668 subjects were planned to receive 3 injections at 0, 6 and 12 months of the CYD dengue vaccine and (2) 1334 subjects were to receive either one injection of a rabies vaccine (Verorab®) followed by 2 injections of a placebo at 6 and 12 months (50 children) or 3 injections, 6 months apart, of a placebo (1284 children). The statistical analysis for the other objectives was descriptive.

Results
The study reported a total of 78 VCD incidences occurring from 28 days post-injection 3 to the end of the Active Phase in 77 subjects (45 in CYD Dengue and 32 in Control). The post-dose 3 VE estimate against any dengue serotype was 30.2% (95% CI: −13.4;56.6). The primary endpoint was not met. The lower bound of the 95% CI of VE was less than 0. However, 91.5% of subjects were seropositive against all 4 serotypes, after the third vaccination. The relative risk of VCD incidence by serotypes was 0.388 (95%CI: 0.179, 0.826) for serotype 1, 0.965 (95% CI: 0.595;1.60) for serotype 2, 0.181 (95% CI: 0.042, 0.612) for serotype 3, and 0.100 (95%CI: 0.002;0.894) for serotype 4 (CSR CYD23, page 41).

Conclusion
The VE against any serotype was less than anticipated and the primary objective of efficacy was not reached. The VE against serotype 2 was 0.035 (95%CI: -0.60;0.405), driving the overall VE

result. It was reported that most of the serotypes of VCD cases identified were serotype 2 (Clinical Overview, section 4.2.2.1).

7. Integrated Efficacy and Immunogenicity

7.1 Efficacy

The two large phase III pivotal studies CYD14 (N=10,275 subjects aged 2-14 years) and CYD15 (N=20,869 subjects aged 9-16 years) were conducted in endemic regions of Asia and Latin America, respectively, using active surveillance to detect dengue diseases. In these two studies together 19,282 subjects (6709 in CYD14 and 12,573 in CYD15) aged 2-16 years received 3 injections of the CYD Dengue vaccine 6-month apart and comprised the Per-Protocol set for efficacy (PPSE). The PD3 VE results from CYD14 and CYD15 were respectively 56.5% (95%CI: 43.8;66.4) and 60.8% (95%CI: 52.0; 68.0) (Table 17).

Table 17: Vaccine efficacy against symptomatic virologically-confirmed dengue cases post-dose 3 due to any of the 4 serotypes - PPSE

Studies	Parameter	CYD Dengue Vaccine Group	Control Group
CYD14	**Number of subjects**	6709	3350
	Number of cases (Number of episodes)	117 (117)	133 (134)
	Number of person-years at risk	6525	3227
	Density incidence (95% CI)	1.8 (1.5; 2.1)	4.1 (3.5; 4.9)
	Vaccine Efficacy (95% CI)		56.5 (43.8; 66.4)
CYD15	**Number of subjects**	12573	6261
	Number of cases (Number of episodes)	176 (176)	221 (221)
	Number of person-years at risk	11792	5809
	Density incidence (95% CI)	1.5 (1.3; 1.7)	3.8 (3.3; 4.3)
	Vaccine Efficacy (95% CI)		60.8 (52.0; 68.0)
CYD14+CYD15	**Vaccine Efficacy (95% CI)**	59.2 (52.3; 65.0)	

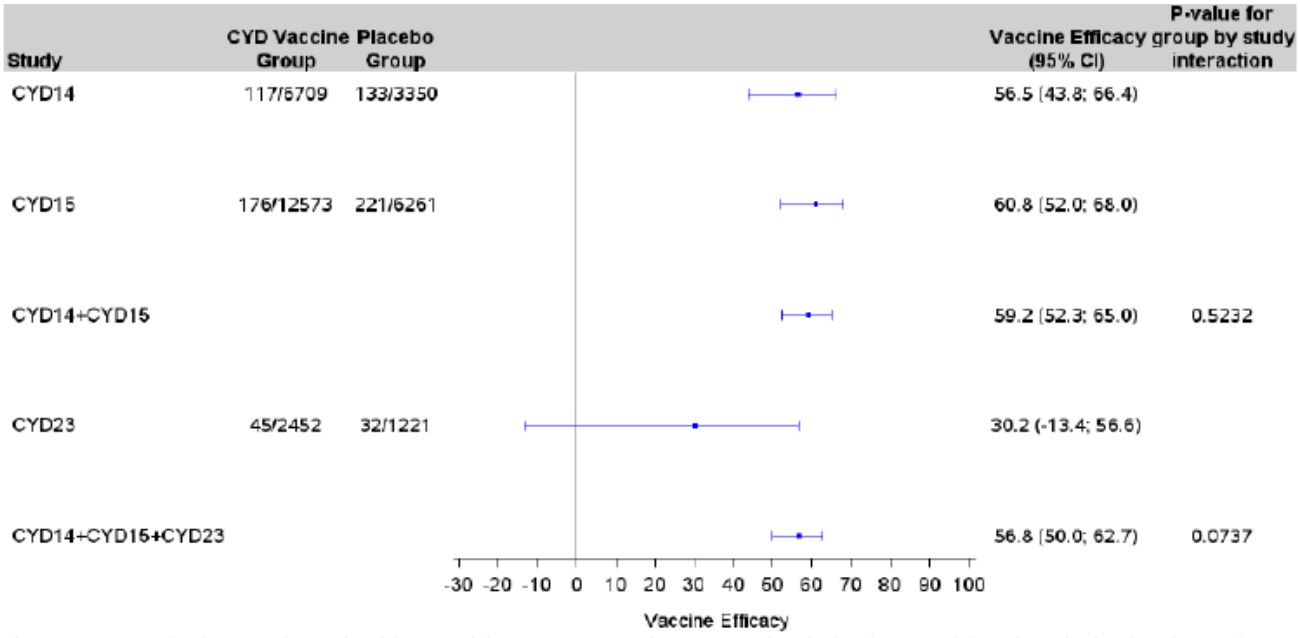
Cases: number of subjects with at least one symptomatic virologically-confirmed dengue episode in the considered period
n Episodes: number of symptomatic virologically-confirmed dengue episodes in the considered period
Density incidence: cases per 100 person-years at risk
CIs for VE on individual studies are calculated using the Exact method.
Integrated Vaccine Efficacy and CIs are calculated using Cox regression model
Source: Adapted from Efficacy Integrated Analysis Report, Table 3.2.1.1, page 86/1365.

Prior to the initiation of CYD14 and CYD15, a proof of concept efficacy study CYD23, was conducted by the Applicant in a relatively smaller-size of 4,002 subjects aged 4-11 years in Thailand. The Applicant noted that the study had "differences in dengue case definitions and laboratory methods and testing algorithm" (Clinical Overview, section 4.2, page 56). With 78 VCD episodes observed in 77 subjects, the study reported that the observed VE point estimate post-dose3 against any serotype was 30.2% (95% CI: -13.4;56.6) (Figure 2). The primary endpoint was not met. Most of the VCD cases in this study were stated to be identified as serotype 2: "32 VCD cases in the Dengue Group and 19 VCD cases in the Control Group were due to serotype 2"（Clinical Overview, page 56-58).

The Applicant also stated, “In both studies, the Active Phase was conducted with high compliance to the protocol with more than 95% of subjects receiving the full 3-injection vaccination schedule and completing the 2-year active surveillance period. In terms of dengue detection in CYD14 and CYD15, around 90% of the febrile episodes reported had an acute sample collected within the first 5 days after the onset of fever, as requested in the protocol, and less than 2% of febrile episodes had no blood specimen for virological confirmation. With regard to dengue incidence in the Control Group during the conduct of the Active Phase, it was higher than incidence rates reported by the passive surveillance systems in the municipalities where the studies are conducted” (Clinical Overview, page 58).

The submission further mentioned that in CYD14, the Control group reported dengue incidence of 4.7% compared to 1.3% from passive surveillance, with respective comparison being 2.9% vs 0.64% in CYD15’s Control (Clinical Overview, page 58-59). All these reflect the high degree of rigor in Applicant’s active surveillance over local government’s passive surveillance.

Figure 2: Forest plot for VE against symptomatic VCD cases PD3 due to any of the 4 serotypes - PPSE



Source: Summary of Clinical Efficacy, page 170 of 358

The Applicant provided integrated efficacy rate from CYD14 and CYD15 for post-dose 3 (Table 17) and Active Phase (Table 18). This integration seems more meaningful than integration with the proof of concept study (CYD23), due to the facts mentioned in the two paragraphs above and as well due to the differences in dengue case definitions, laboratory methods and testing algorithm. Also, the BLA reports that the efficacy studies CYD14 and CYD15 “had consistent results with a heterogeneity test of 0.5235, i.e., p-value ≥ 10%”. The heterogeneity test showed a p-value < 10% with CYD23 pooled (ref. Summary of Clinical Efficacy, page 152). It appears pooling with CYD23 causes significant heterogeneity. This also can be discerned from the forest plot in Figure 2. In the Forest plot, the numerator is the number of subjects with a symptomatic VCD episode in the considered period. The denominator is the number of subjects. VE of a study is calculated using density incidence: cases per 100 person-years at risk. Integrated VEs and CIs were calculated using Cox regression models.

The integrated VEs against VCD due to any serotypes in post-dose 3 and Active Phase were respectively, 59.2% (95%CI: 52.3; 65.0) (Table 17) and 60.3% (55.7; 64.5) (Table 18).

Table 18: Vaccine Efficacy against symptomatic virologically-confirmed dengue cases during the whole Active Phase due to any of the 4 serotypes - FASE

Studies	Parameter	CYD Dengue Vaccine Group	Control Group
CYD14	**Number of subjects**	6848	3424
	Number of cases (Number of episodes)	286 (290)	309 (319)
	Number of person-years at risk	13571	6623
	Density incidence (95% CI)	2.1 (1.9; 2.4)	4.7 (4.2; 5.2)
	Vaccine Efficacy (95% CI)		54.8 (46.8; 61.7)
CYD15	**Number of subjects**	13914	6940
	Number of cases (Number of episodes)	277 (280)	385 (388)
	Number of person-years at risk	26883	13204
	Density incidence (95% CI)	1.0 (0.9; 1.2)	2.9 (2.6; 3.2)
	Vaccine Efficacy (95% CI)		64.7 (58.7; 69.8)
CYD14+CYD15*	**Vaccine Efficacy (95% CI)**	60.3 (55.7; 64.5)	

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: cases per 100 person-years at risk
Integrated Vaccine Efficacy and CIs are calculated using Cox regression model
Source: Efficacy Integrated Analysis Report, Table 3.3.2.1, page 98/1365

Earlier it was seen in each individual pivotal study that the VE reduced in subjects with baseline dengue non-immune status (Table 4 and Table 10). From integrated results based on subjects aged 9-16 years, the VEs post-dose3 were 79.4% (95%CI:58.4, 89.8) for baseline dengue immune subjects and 42.7% (95% CI: -41.1; 76.8) for baseline dengue non-immune subjects (Table 19). For VEs in the Active Phase, these VEs were respectively 81.9% (95% CI: 67.2%; 90.0%) and 52.5% (95% CI: 5.9; 76.0) (Table 20). In the context of VEs post-dose3 in baseline PRNT dengue non-immune subjects, reference can be made to similarly computed VEs for subjects classified as dengue seronegative based on NS1 testing of M13 serum samples (*Dengue seronegative subjects by anti-NS1 ELISA and baseline PRNT*, subsection in 7.2)

The younger vaccinees aged 2-5 years presented high risk (> 5-fold) for hospitalized VCD cases in post-dose 3, compared to adolescents 12-16 years old. As seen from Table 21, the incidence densities for 2-5 years old vs adolescent vaccinees were 0.5 (95% CI: 0.3;0.8) vs <0.1 (95%CI: 0.0;0.3). Also, in the logistic regression of VCD cases from post-dose3 to the end of trial (ref. Table 3.5.3.35, Efficacy Integrated Analysis Report, page 677), the observed regression coefficient was 3.247 (95% CI: 1.060;5.433) which, after exponentiation, implied high RR value. All this made younger subjects, overall under 9 years of age, a high-risk group for hospitalization and thus were excluded from CYD14 in Table 19 and Table 20. Also, the proposed package insert does not include subjects under 9 years old in age indication.

Table 19**:** VE against symptomatic VCD cases PD3 due to any of the 4 serotypes for subjects 9 through 16 years by baseline dengue status, FASI

		Dengue immune		Dengue non Immune	
Studies	**Parameter**	**CYD Vaccine Group**	**Control Group**	**CYD Vaccine Group**	**Control Group**
CYD14	**Number of subjects**	483	250	127	58
	Number of cases (Number of	4 (4)	9 (9)	4 (4)	3 (3)
	Number of person-years at risk	471	241	124	55
	Density incidence (95% CI)	0.9 (0.2; 2.2)	3.7 (1.7; 7.0)	3.2 (0.9; 8.1)	5.5 (1.1; 15.1)
	Vaccine Efficacy (95% CI)	77.2 (18.3; 94.9)		40.6 (-305.4; 90.0)	
CYD15	**Number of subjects**	1034	492	248	140
	Number of cases (Number of	7 (7)	17 (17)	6 (6)	6 (6)
	Number of person-years at risk	1002	472	236	131
	Density incidence (95% CI)	0.7 (0.3; 1.4)	3.6 (2.1; 5.7)	2.5 (0.9; 5.5)	4.6 (1.7; 9.7)
	Vaccine Efficacy (95% CI)	80.6 (50.7; 93.2)		44.5 (-107.8; 85.1)	
CYD14+CYD15	**Vaccine Efficacy (95%CI)**	79.4 (58.4; 89.8)		42.7 (-41.1; 76.8)	

Baseline dengue immune subjects are defined as those subjects with titers >= LLOQ (i.e. 10) (1/dil) against at least one dengue serotype at baseline. Subjects with undetermined baseline status (no titer >= LLOQ and at least one missing titer) are excluded. Immunoassays are Dengue PRNT.
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.
Source: 5.3.5.3 Additional Statistical Analysis, Table 2 1, page 323 of 366.

Table 20: VE against symptomatic VC dengue cases during the whole Active Phase due to any of the 4 serotypes by baseline dengue status in subjects aged 9 to 16 years - FASI

		Dengue Immune		Dengue Non-immune	
Studies	**Parameter**	**CYD Dengue Vaccine**	**Control Group**	**CYD Dengue Vaccine**	**Control Group**
CYD14	**Number of subjects**	487	251	129	59
	Number of cases (Number of episodes)	7 (7)	17 (18)	7 (8)	8 (8)
	Number of person-years at risk	981	496	256	112
	Density incidence (95% CI)	0.7 (0.3; 1.5)	3.4 (2.0; 5.4)	2.7 (1.1; 5.6)	7.1 (3.1; 13.6)
	Vaccine Efficacy (95% CI)	79.2 (47.2; 92.7)		61.6 (-21.1; 88.1)	
CYD15	**Number of subjects**	1073	512	258	149
	Number of cases (Number of episodes)	8 (8)	23 (23)	9 (9)	9 (9)
	Number of person-years at risk	2116	994	500	284
	Density incidence (95% CI)	0.4 (0.2; 0.7)	2.3 (1.5; 3.5)	1.8 (0.8; 3.4)	3.2 (1.5; 5.9)
	Vaccine Efficacy (95% CI)	83.7 (62.2; 93.7)		43.2 (-61.6; 80.0)	
CYD14+ CYD15	**Vaccine Efficacy (95% CI)**	81.9 (67.2; 90.0)		52.5 (5.9; 76.1)	

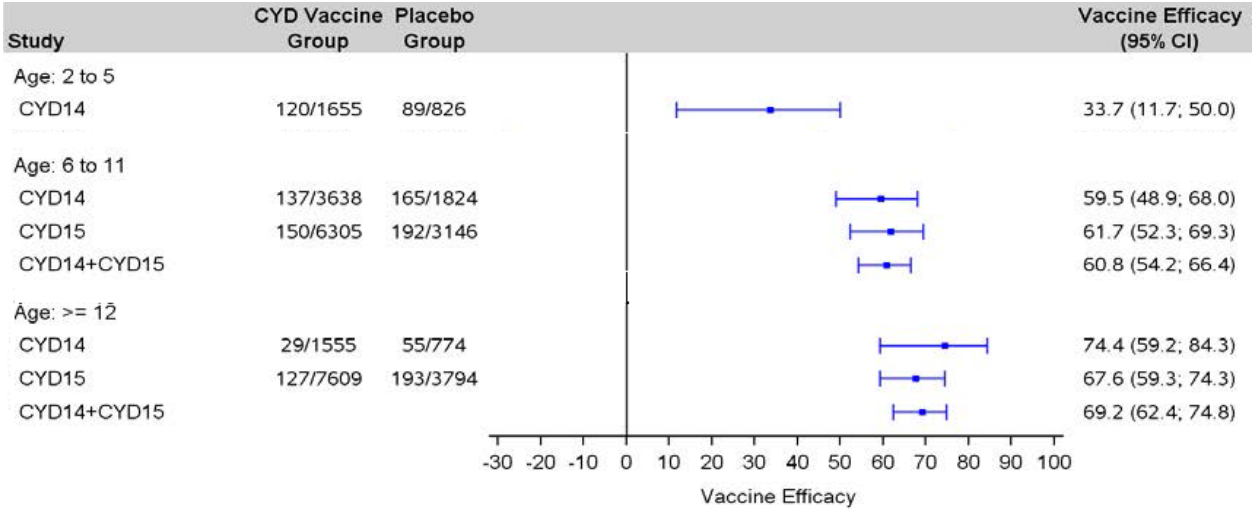
Baseline dengue immune subjects are defined as those subjects with titers >= LLOQ (i.e. 10) (1/dil) against at least one dengue serotype at baseline.
Subjects with undetermined baseline status (no titer >= LLOQ and at least one missing titer) are excluded. Immunoassays are Dengue PRNT.
Cases: number 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.
Integrated Vaccine Efficacy and CIs are calculated using Cox regression model.
Source: Integrated Efficacy Analysis Report, Table 3.6.5.15, page 760

Vaccine Efficacy and Age

The Applicant reported VE (95%CI) of 45.7% (17.2; 64.3) for age 2-5 years in CYD14, 56.2% (45.9; 64.5) for age 6-11 years in CYD14/CYD15 integrated and 68.7% (59.1; 76.0) for 12-16 years, also, in CYD14/CYD15 integrated, against VCD of any serotypes in the post-dose 3 period (Efficacy Integrated Analysis Report, Page 180 of 1365). More or less similar trend in VE was noticed in the Active Phase as well (Figure 3). By looking at the confidence intervals, it

appears that VE was lowest in the 2-5 years age group, and across the two subsequent higher age groups the overall VE might not have varied remarkably.

Figure 3: Forest plot for VE against symptomatic VCD during the whole Active Phase due to any of the 4 serotypes according to age group by study – FASE



Source: Adapted from Summary of Clinical Efficacy page 192 of 358, Figure 25.

Table 21: VE against hospitalized virologically-confirmed dengue cases during the whole Active Phase due to any of the 4 serotypes by age group – FASE

Studies	Parameter	Children 2-5 years		Children 6-11 years		Adolescents	
		CYD Dengue Vaccine Group	Control Group	CYD Dengue Vaccine Group	Control Group	CYD Dengue Vaccine Group	Control Group
CYD14	Number of subjects	1655	826	3638	1824	1555	774
	Number of cases (Number of episodes)	17 (17)	13 (13)	20 (20)	37 (37)	3 (3)	11 (11)
	Number of person-years at risk	3325	1654	7351	3664	3152	1560
	Density incidence (95% CI)	0 5 (0 3; 0 8)	0 8 (0 4; 1 3)	0 3 (0 2; 0 4)	1 0 (0 7; 1 4)	<0 1 (0 0; 0 3)	0 7 (0 4; 1 3)
	Vaccine Efficacy (95% CI)		35.0 (-45.6; 70.3)		73.1 (52.4; 85 2)		86.5 (48.9; 97.6)
CYD15	Number of subjects			6305	3146	7609	3794
	Number of cases (Number of episodes)			8 (8)	22 (22)	9 (9)	21 (21)
	Number of person-years at risk			12278	6107	14805	7389
	Density incidence (95% CI)			<0 1 (0 0; 0 1)	0 4 (0 2; 0 5)	<0 1 (0 0; 0 1)	0 3 (0 2; 0 4)
	Vaccine Efficacy (95% CI)				81.9 (57.8; 93.0)		78.6 (51.3; 91.4)
CYD14+CYD15	Vaccine Efficacy (95% CI)				76.4 (63.0; 84 9)		81.3 (63.8; 90.4)

Cases: number of subjects with at least one hospitalized virologically-confirmed dengue episode in the considered period
n Episodes: number of hospitalized virologically-confirmed dengue episodes in the considered period
Density incidence: cases per 100 person-years at risk
Integrated Vaccine Efficacy and CIs are calculated using Cox regression model
Source. Efficacy Integrated Analysis Report, Table 3.4.5.101, page 471.

7.2 Immunogenicity

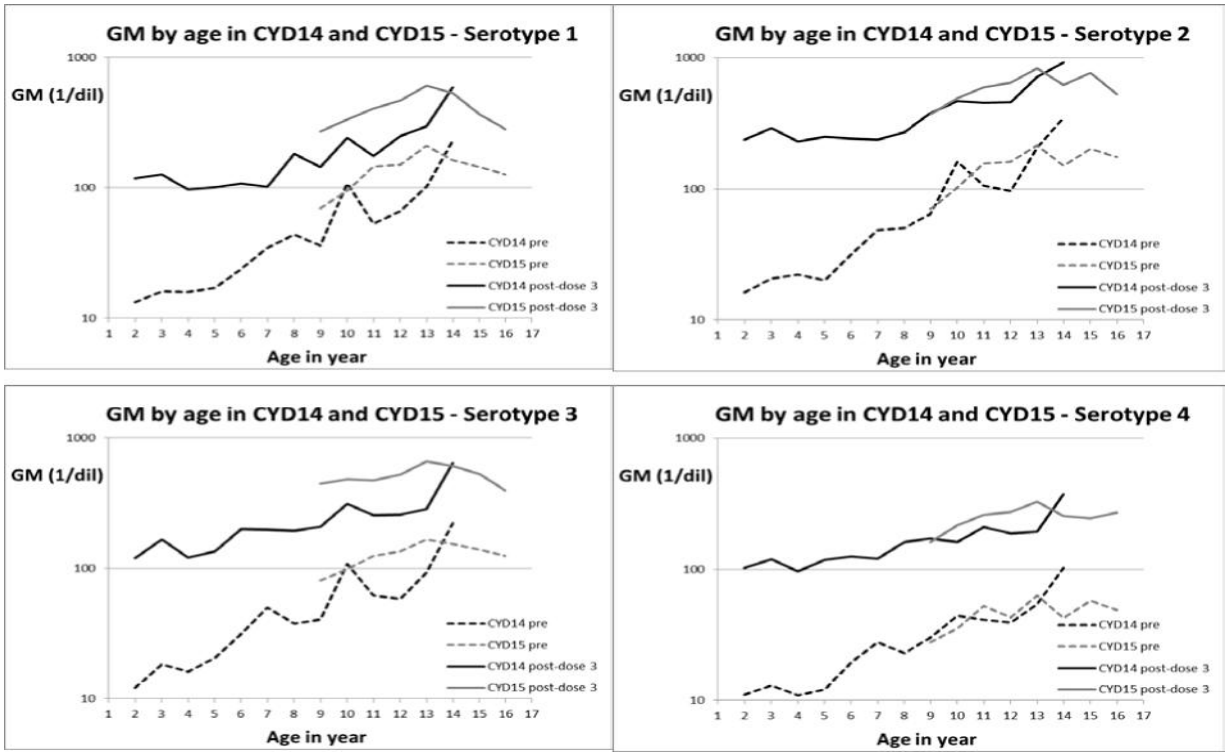
Level and Persistence

Descriptive **s**ummary results of GMTs at pre-injection 1 and at 28 days post-injection 3 from subjects aged 9-17 years in CYD14 and CYD15 are provided in Table 22, by serotype and baseline dengue immune status. GMT information from adult subjects aged 18-45 years from supportive studies (CYD22, CYD28 are CYD47) also included in this table. These supportive studies were briefly described in Table 14.

In all studies, the post-injection 3 GMTs were higher in the baseline dengue immune subjects than the baseline dengue non-immune subjects. Among the baseline dengue immune subjects, the antibody persistence pattern over four years post-injection is shown in Figure 5 for CYD14 and CYD15.

Additionally, the PD3 GMTs were higher with higher GMTs at baseline, in each serotype. Since baseline GMT increase with age, the PD3 GMT also displayed increasing pattern with age (Figure 4).

Figure 4: Geometric means Pre-dose 1 and Post-dose 3 against each serotype in CYD14 and CYD15 according to age - FAS



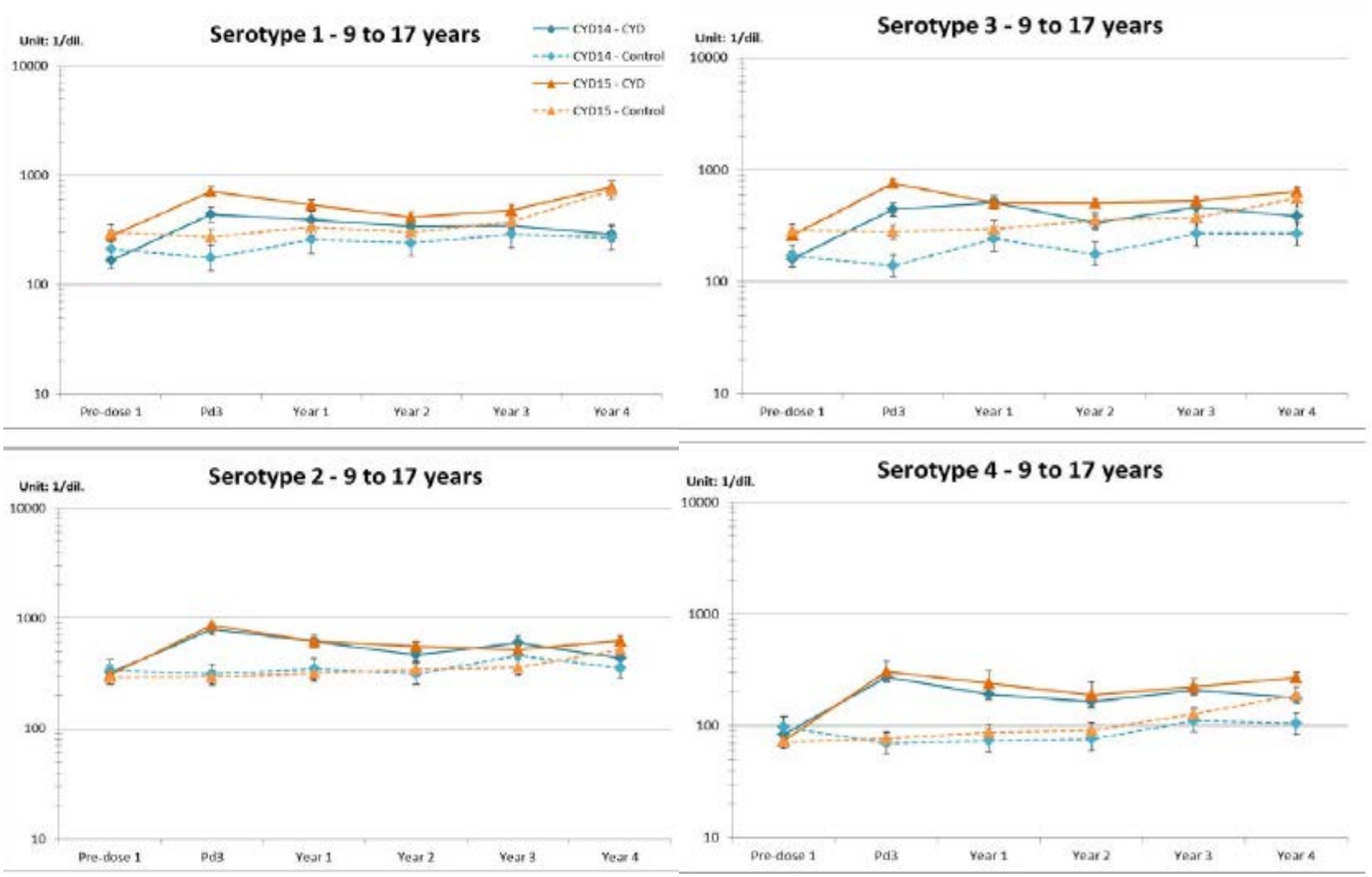
Source: Adapted from Summary of Clinical Efficacy, Figure 5, page 112 of 358.

Table 22: Dengue immunogenicity summary in endemic countries and Phase III efficacy trials pre-injection 1 and post-injection 3 - GMT of Ab against each serotype (1/dil) by baseline dengue status - Dengue PRNT, FASI.

				Serotype 1		Serotype 2			Serotype 3			Serotype 4		
Age group	**Region**	**Study**	**N**	**Pre-injection 1 GM (95% CI)**	**Post-injection 3 GM (95% CI)**	**N**	**Pre-injection 1 GM (95% CI)**	**Post-injection 3 GM (95% CI)**	**N**	**Pre-injection 1 GM (95% CI)**	**Post-injection 3 GM (95% CI)**	**N**	**Pre-injection 1 GM (95% CI)**	**Post-injection 3 GM (95% CI)**
Dengue Immune														
9 to 17 years*	**Endemic AP**	**CYD14**	485	167 (481) (138; 202)	437 (482) (373; 511)	485	319 (482) (274; 373)	793 (481) (704; 892)	485	160 (477) (135; 190)	443 (481) (387; 507)	485	83.8 (483) (72.0; 97.6)	272 (481) (245; 302)
	Endemic LatAm	**CYD15**	1048	278 (1046) (247; 313)	703 (1040) (634; 781)	1048	306 (1048) (277; 338)	860 (1040) (796; 930)	1048	261 (1048) (235; 289)	762 (1040) (699; 830)	1048	73.3 (1046) (66.6; 80.7)	306 (1040) (286; 328)
Adults (18 to 45 years)	**Endemic AP**	**CYD22**	19	408 (19) (205; 810)	785 (17) (379; 1626)	19	437 (19) (240; 797)	937 (17) (586; 1499)	19	192 (19) (117; 313)	482 (17) (357; 651)	19	86.5 (19) (41.2; 182)	387 (17) (253; 591)
		CYD28	66	59.8 (66) (36.8; 97.4)	235 (56) (135; 409)	66	67.1 (66) (40.9; 110)	236 (56) (144; 387)	66	48.4 (66) (32.9; 71.0)	239 (56) (166; 342)	66	22.1 (66) (14.7; 33.4)	211 (55) (155; 287)
		CYD47	109	324 (109) (236; 445)	688 (98) (524; 901)	109	363 (109) (269; 490)	644 (98) (509; 814)	109	394 (109) (299; 519)	961 (98) (763; 1211)	109	80.7 (109) (61.3; 106)	413 (98) (331; 516)
Dengue Non-immune														
9 to 17 years*	**Endemic AP**	**CYD14**	128	5.00 (128) (NC)	33.3 (127) (25.7; 43.0)	128	5.00 (128) (NC)	114 (126) (88.8; 146)	128	5.00 (128) (NC)	57.9 (126) (45.0; 74.4)	128	5.00 (128) (NC)	63.0 (127) (49.9; 79.6)
	Endemic LatAm	**CYD15**	251	5.00 (251) (NC)	35.3 (249) (29.8; 41.9)	251	5.00 (251) (NC)	105 (249) (89.3; 125)	251	5.00 (251) (NC)	93.6 (249) (80.3; 109)	251	5.00 (251) (NC)	89.5 (249) (76.1; 105)
Adults (18 to 45 years)	**Endemic AP**	**CYD22**	1	5.00 (1) (NC)	89.0 (1) (NC)	1	5.00 (1) (NC)	95.0 (1) (NC)	1	5.00 (1) (NC)	47.0 (1) (NC)	1	5.00 (1) (NC)	219 (1) (NC)
		CYD28	74	5.00 (74) (NC)	14.6 (64) (11.3; 18.8)	74	5.00 (74) (NC)	26.4 (64) (19.2; 36.3)	74	5.00 (74) (NC)	39.1 (64) (30.5; 50.1)	74	5.00 (74) (NC)	79.5 (64) (55.9; 113)
		CYD47	17	5.00 (17) (NC)	46.1 (17) (23.7; 89.7)	17	5.00 (17) (NC)	94.3 (17) (36.6; 242)	17	5.00 (17) (NC)	123 (17) (69.3; 218)	17	5.00 (17) (NC)	103 (17) (74.5; 141)

*Subjects included in CYD14 and CYD15 were 9 through 16 years old.
Source: Clinical Overview, Table 4, page 47 of 120.

Figure 5: Summary of persistence of GMTs of dengue Abs against each serotype with the parental dengue virus strains in baseline dengue immune subjects 9 through 16 years - Dengue and Control Groups - FASI



Source. Adapted from Clinical Overview, Figure 4, page 50-51

Immunogenicity and Efficacy

Table 23 provides case and noncase GMTs post-dose 3 by study group and serotype, in CYD14 and CYD15. Also provided are the descriptive, reverse cumulative distribution curves of PRNT titer in Figure 6. From Table 23, it follows in both studies that

(1) the GMTs (95% CI) were higher for the noncase subjects compared to cases, for each serotype and study group, and
(2) the case and noncase GMTs (95% CI) in the CYD vaccine group were higher compared to the respective case and noncase GMTs (95%CI) in the Control group, for each serotype.

Table 23: Geometric means Post-dose 3 for each serotype for dengue cases and non-cases subjects from CYD14 and CYD15 during the Active Phase – mFASE

	Dengue Group Cases M	Dengue Group Cases GMT (95% CI)	Dengue Group Noncases M	Dengue Group Noncases GMT (95% CI	Control Group Cases M	Control Group Cases GMT (95% CI)	Control Group Noncases M	Control Group Noncases GMT (95% CI
CYD14	N=6772				N=3379			
Serotype 1	50	58.1	1275	167	47	11.8	604	44.7
		(41.9; 80.4)		(150; 185)		(8.07; 17.2)		(36.8; 54.3)
Serotype 2	36	129	1273	352	26	23.8	604	61.8
		(92.5; 179)		(324; 382)		(12.6; 45.0)		(51.3; 74.6)
Serotype 3	10	77.5	1273	208	23	22.7	604	40.0
		(49.6; 121)		(190; 228)		(14.0; 36.6)		(33.8; 47.3)
Serotype 4	17	61.7	1274	150	34	13.7	604	24.3
		(32.9; 116)		(140; 161)		(8.85; 21.1)		(21.1; 28.0)
CYD15	N=13288				N=6643			
Serotype 1	65	50.2	1274	407	66	12.3	608	125
		(34.6; 72.9)		(364; 454)		(8.81; 17.2)		(104;150)
Serotype 2	58	69.7	1274	584	49	44.5	608	128
		(46.9; 103)		(537; 635)		(26.3; 75.2)		(108; 152)
Serotype 3	43	239	1274	519	82	37.9	608	125
		(177; 324)		(475; 567)		(27.1; 53.0)		(105;149)
Serotype 4	18	77.6	1274	244	39	15.5	608	45.6
		(43.1; 140)		(228; 262)		(10.8; 22.3)		(39.6; 52.5)

M: number of subjects with available data for the relevant endpoint.
Cases are subjects with at least one VCD case between 28 days post-injection 3 and the end of the active phase due to the considered serotype.
Non cases are subjects in the immunogenicity subset who do not have VCD due to any serotype from D0 to the end of the Active Phase.
Source: Summary of Clinical Efficacy, page 243 of 358

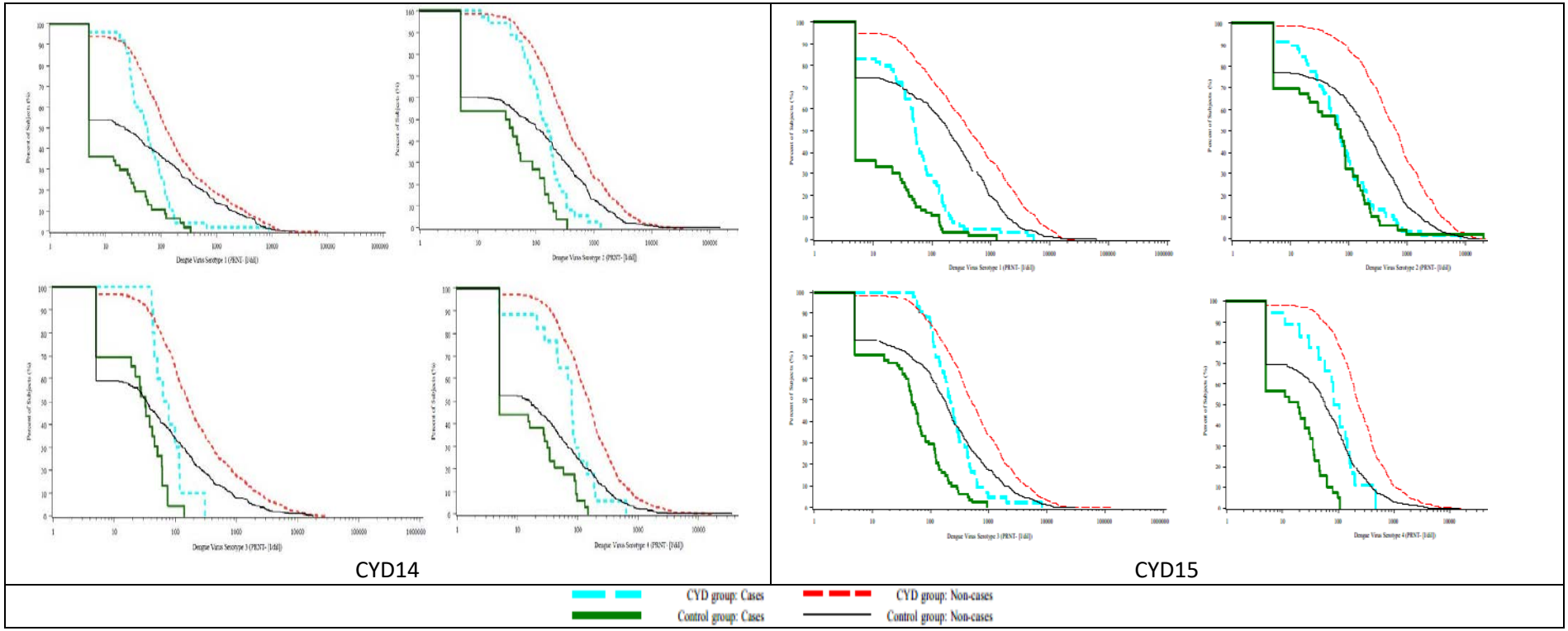
By looking at the case and noncase GMTs (95% CI), it appears that one threshold of titer as protection-correlate existed in the CYD dengue group and another different threshold of lower titer existed in the Control group. For example, in the first row showing serotype 1 CYD14, a threshold existed between the case and noncase GMTs of 58.1 and 167.0, respectively, in the Dengue CYD group; with a different, lower threshold between corresponding GMTs of 11.8 and 44.7 in the Control group. For a given group of CYD vaccine or Control, and for each serotype, the 95% CIs of GMTs did not overlap. Similar pattern is observed for each serotype and study. The difference in thresholds between the CYD vaccine and Control groups, rather than a single

unique threshold in the titer spectrum, does not allow identification of a protection threshold. This, in other words, means that protection is not fully mediated through PRNT titer.

The earlier results (Table 17, Table 18) showed that the VCD incidence reduced in the CYD vaccine group. The features (1) and (2) above imply that the VCD incidence is less likely as well with increased titer, where the extent of increase depends on which study arm the titer is from. The Applicant's logistic regression analyses (Table 24), which aim for risk-factor detection rather than prediction of protection level, show that there were significant effects on VCD incidence from vaccine group in addition to titer, indicating that the increased titer alone, unless informed by vaccine group, is not enough to explain VCD risk. The logistic regression models, however, may not have presented good predictive power (last row, Table 24).

The Applicant juxtaposed the pre-injection 1 and post-injection 3 GMT results of subjects aged 9-17 years (CYD14, CYD15) with those from adult subjects aged 18-45 years (Table 22) and contended that "overall antibody levels at baseline and post-Injection 3 titers were higher in adults than in subjects 9 to 17 years from the same endemic regions." (Clinical Overview, page 48 of 120). Such comparison is at best descriptive because the studies on adults (CYD22, CYD28 and CYD47) were not designed or did not have pre-specified criterion for such comparison. The adults also had limited sample sizes. The VRBPAC (March 7, 2019) also had concern about the adult studies, did not support immuno bridging of adults with the pivotal efficacy children and adolescent subjects, and the Applicant decided to not pursue vaccine's indication for age 17 and above.

Figure 6: Reverse cumulative distribution curves for each serotype (PRNT assay) 28 days PD3 for cases and non-dengue case subjects during the Active Phase- mFASE



Note: Given any study protocol, in the first panel, the first set and second set of graphs represent serotype1 and serotype 2, respectively, while in the 2nd panel the same ordered sets represent serotype 3 and serotype 4 respectively. Vertical axis represents percent of subjects (%) and horizontal represents PRNT titer.

Source: Adapted from Figure 39 and Figure 40, Summary of Clinical Efficacy, page 246-247.

Table 24: Summary of meta-analysis logistic models for symptomatic VC dengue cases from PD3 until the end of Active Phase per serotype – mFASE - CYD14 and CYD15

	Logistic Model			
	p-values			
Covariates	VCD cases Serotype 1	VCD cases Serotype 2	VCD cases Serotype 3	VCD cases Serotype 4
Homologous PD3 Log10PRNT	< 0.0001	< 0.0001	< 0.0001	0.0002
Study	0.0001	< 0.0001	< 0.0001	not kept
Vaccine Group	NS	< 0.0001	< 0.0001	0.7276
Age Groups:				
2-5 vs 12-16*	0.0128	0.0384	0.3405	0.0110
6-11*† vs 12-16	0.0875	0.5441	0.0032	0.6761
Interactions between PRNT PD 3 titers	With age groups (2 to 5 years, 6 to 11years)	With vaccine group and age groups (2 to 5 years)	none	With vaccine group and age group (2 to 5 years)
Interactions between PRNT PD3 titers	With age groups (2 to 5 years, 6 to 11 years)	With vaccine group and age groups (2 to 5 years)	none	With vaccine group and age groups (2 to 5 years)
Pseudo R^2 (Cox&Snell method)[z]	0.0419	0.0302	0.0229	0.0233

Logistic Models: it models the probability of dengue according to the log10 of Ab titers of the homologous serotype and then of the 4 serotypes, vaccine group, study, age, gender, study by vaccine group interaction, and all two-ways interaction including Ab titers of the studied serotype.
If an interaction p-value is <0.10, all the associated covariates are kept in the model, even if their p-value is ≥ 0.10. Interactions p-values (Wald test) are included in the source tables.

* 12-14y for CYD14 as per study design
† 9-11y for CYD15 as per study design
NS: Not Significant
[z]VCD cases of serotype explained by log10 of titer of serotype and vaccine group
(ref. Table 3.5.2.6: Efficacy Integrated Analysis Report, page 584)
Source: Adapted from Summary of Clinical Efficacy, page 259 of 358

Dengue seronegative subjects by anti-NS1 ELISA and baseline PRNT

The Applicant also performed NS1 Supplemental Analysis. Using a newly developed assay Dengue anti-NS1 IgG ELISA, a surrogate for baseline dengue serostatus (assay threshold of 9 EU/mL) was worked out from post-dose 3 (M13) blood samples. The VE evaluation then proceeded in a case-cohort design, where the cases were as observed in the study and the cohort consisted of a random sample of 10% of all subjects who provided post-dose 3 blood specimens. The case-cohort design is due to Prentice (ref. Prentice RL. A case-cohort design for epidemiological cohort studies and disease prevention trials. Biometrika.1986; 73 (1):1-11). "The overall percentage agreement between PRNT50 at baseline and the anti-NS1 assay at M13 was 87.05% (2514/2888) with a kappa coefficient of 0.613 (95% CI: 0.578, 0.648). In the CYD Vaccine Group, the kappa coefficient of 0.561 (95% CI: 0.516, 0.607) was lower than the concordance observed in the Placebo Group (kappa coefficient of 0.707; 95% CI: 0.654, 0.760)" (ref. Additional Report, page 24 of 431). These numbers were updated by the Applicant in NS1 extension analysis and the corresponding update figures were 88.5% (3240/3863), 0.696 (95% CI: 0.670, 0.722), 0.659 (95% CI: 0.626, 0.693), and 0.765 (95% CI: 0.725, 0.805) (ref.

Additional CSR, NS1 Extension, page 86 of 821). This review did not focus much on the NS1 based supplemental analyses, except for post-dose3 VEs in baseline seronegative subjects.

For Dengue non-Immune subjects by PRNT 50 at baseline, the VEs post-dose3 for CYD14, CYD15 and CYD14+CYD15 were respectively 40.6% (95%CI: -305.4; 90.0), 44.5% (95%CI: -107.8; 85.1) and 42.7% (95%CI: -41.1; 76.8) (Table 19). The corresponding figures for subjects classified as dengue seronegative based on NS1 testing of M13 serum samples were 57% (95%CI: -28.6, 85.6), -0.9% (95%CI:-63.9, 37.8) and 11.2% (95%CI:-38.2, 42.9) (Additional CSR (NS1) Version 1.0, Table 6.2, page 55 of 431). There seemed to be marked differences in these VE point estimates between PRNT baseline dengue non-immune status and NS1 based classification of dengue seronegative at M13. However, in both assessments, very wide 95%CIs extending from negative to positive ranges were present.

An NS1 extension analysis was developed to address potential limitations that the Applicant contended were present in the original NS1 supplemental analysis. These limitations included imperfect representativeness of the original sub-cohort due to shorter enrollment period of the immunogenicity subset in CYD14 and CYD15 than that of the entire corresponding studies, and gaps due to a lack of accounting for Month 0- 13 cases. The VEs post-dose 3 to the end of active phase in subjects ≥9 years and classified as seronegative by measured/imputed PRNT50 at baseline for CYD14, CYD15, and CYD14+CYD15 were respectively 50% (-125%, 89%), 33% (3, 57%) and 37% (3%, 59%) using the targeted maximum likelihood estimation method, or 69.8% (10.3%, 89.8%), 35.8% (-17.2, 64.8%), and 42.8% (-1.4%, 67.7%) using the multiple imputation method (Additional CSR (NS1 Extension), Version 1.0, Table 6.11, Page 109-110 of 821). These results were more consistent with VE point estimates based on the immunogenicity subset using measured PRNT baseline serostatus. However, the observed VE estimates were not consistent across different methods, indicating that there might be limited VE, if any, for seronegative subjects.

7.3 Review Summary

Efficacy

1. The post-dose 3 vaccine efficacy (VE) estimate was 56.5% (95%CI: 43.8; 66.4) in pivotal study CYD14 and 60.8% (95% CI: 52.0; 68.0) in pivotal study CYD15. Integrating these two studies, the CYD dengue vaccine demonstrated an overall reduction of 59.2% (95%CI: 52.3; 65.0) in VCD incidences due to any serotype and severity post-dose3 in Active Phase. The confidence lower bounds of VE exceeded the pre-specified 25% limit, supporting that the primary objective of efficacy was met in both pivotal studies individually and as well in integrated results.

2. In exploratory analyses, the VE estimates against VCD post-dose 3 appeared to have varied by subject's age, the lowest being 45.7% (95% CI: 17.2;64.3) for age 2-5 years (CYD14), and 56.2% (95% CI: 45.9; 64.5) and 68.7% (95% CI: 59.1;76.0) for age 6-11 years and 12-16 years, respectively, from CYD14+CYD15 integrated results (Efficacy Integrated Analysis Report, Table 3.4.5.1, Page 180 of 1365). The observed trend in VE estimates with age more or less held in the Active Phase also (Figure 3). By looking at the confidence intervals, it appears that VE's

increasing trend, although started from 2-5 years age group, did not appear to be very dominant across the two subsequent higher age groups.

3. The CYD dengue vaccine reduced overall incidences of VCD in the Active Phase also. The VEs in individual studies CYD14 (subjects age 2-14 years) and CYD15 (9-16 years) were 54.8% (95%CI: 46.8; 61.7) and 64.7% (95%CI: 58.7; 69.8), respectively, and 60.3% (95% CI: 55.7; 64.5) after integration (Table 18).

4. The reduction of VCD incidences post-dose 3 and in Active Phase was observed for all serotypes. For serotype 1 and serotype 2, however, the confidence lower bounds of VE showed instances of being negative or falling under the 25% limit (Table 3 and Table 9). The analysis of VEs by serotype was not powered in the study and as such is descriptive.

5. The overall VEs were higher in baseline dengue immune subjects compared to the baseline dengue non-immune subjects (Table 4 and Table 10). For the baseline dengue immune versus non-immune subjects, the VEs post-dose3 from integrated results were respectively 79.4% (95%CI: 58.4; 89.8) and 42.7% (95%CI: -41.1; 76.8) in subjects aged 9-16 years (Table 19). For the same comparison during the Active Phase, the corresponding VEs were 81.9 (95%CI: 67.2; 90.0) and 52.5 (95%CI: 5.9; 76.1), respectively (Table 20).

6. The CYD dengue vaccine reduced hospitalized VCD cases by 78.6% (95% CI: 57.0; 90.0) in the post-dose 3 period and 80.3% (95% CI: 65.0; 89.0) in the Active Phase period, in CYD15. In CYD14, these respective VEs were 71.4% (95% CI: 49.0;84.0) and 67.0% (95% CI: 50.0;79.0). Reduction was also seen in VCD cases meeting WHO criteria, with VE $\geq$ 80% regardless of periods and in both pivotal studies.

7. The basic data (Table 23) on GMT at post-dose 3 and subsequent VCD outcomes during the Active Phase provide useful information on the relationship between Ab titers and efficacy. In both studies CYD14 and CYD15, (1) the GMTs (95% CI) were higher in noncase subjects compared to cases, for each serotype and study group and (2) the case and noncase GMTs (95% CI) in the CYD dengue group were higher compared to the respective GMTs (95%CI) in the Control group. The case and noncase GMTs had non-overlapping CIs, given a study group and serotype. For serotype 3 in the Control group, however, the overlapping was narrow. The feature (1) implies a trend for higher titer in noncases over cases in general, and feature (2) implies different titer thresholds for different study groups, with lower titer threshold being in the Control group. The increase in titer in VCD noncases, as observed from Table 23, differed by treatment group. The findings held as well in the Applicant's logistic regression modeling of VCD cases showing statistical significance for both titer and treatment group (Table 24). The models, however, may not have presented good predictive power (last row, Table 24). The Applicant's results presenting significance of treatment group corroborates that PRNT titer alone is not adequate to explain efficacy.

8. In view of the above, bridging of PRNT titer may not necessarily infer bridging of efficacy. Additionally, the studies for the adults immunogenicity data did not have design pre-specifications for comparison with the CYD14/CYD15's immunogenicity data on 9-16 years old subjects and had limited sample size. The comparison is post-hoc and is difficult to interpret statistically. It can be viewed as descriptive only.

9. For Dengue non-Immune subjects aged 9-16 years by PRNT at baseline, the VE post-dose3 for CYD14+CYD15 was 42.7% (95%CI: -41.1; 76.8) (Table 19). The corresponding figure for subjects classified as dengue seronegative based on NS1 testing of M13 sera was 11.2% (95%CI: -38.2, 42.9) (Additional CSR (NS1) Version 1.0, Table 6.2, page 55 of 431). There seemed to be marked difference in VE point estimates between PRNT baseline dengue non-immune status and NS1 based classification of dengue seronegative using sera at M13. But in both assessments, the wide 95%CIs extending from negative to positive ranges were consistently present.

In an NS1 extension analysis described previously, the VEs in subjects classified as seronegative by measured/imputed PRNT50 at baseline for CYD14, CYD15, and CYD14+CYD15 were respectively 50% (-125%, 89%), 33% (3, 57%) and 37% (3%, 59%) using the targeted maximum likelihood estimation method, or 69.8% (10.3%, 89.8%), 35.8% (-17.2, 64.8%), and 42.8% (-1.4%, 67.7%) using the multiple imputation method (Additional CSR (NS1 Extension), Version 1.0, Table 6.11, Page 109-110 of 821).

Immunogenicity

10. The GMTs in CYD dengue vaccinees increased from the pre-injection 1 level to post-injection 2 and to post-injection 3 for all 4 serotypes. During the first year post-dose 3 and in subsequent years, these GMTs declined, but maintained all along the higher level above baseline and Control level. Additionally, the proportion of subjects seropositive (i.e., titers $\geq$ 10(1/dil)) at 4 years post-dose 3 persisted at high level regardless of serotype. The seropositive rates ranged from 79.2% to 89.6% in CYD14 and from 88.7% to 94.2% in CYD15, for all serotypes.

11. Post-dose 3 GMT was influenced by baseline dengue immune status. The post-dose 3 GMTs were higher among baseline dengue immune subjects compared to those who were dengue non-immune at baseline. Such influence coupled with increased exposure with age can make GMT to increase with age, a pattern provided in Figure 4.

12. In lot consistency evaluation, where the criterion required that, in all lot-pairs, the GMT ratios be contained within the equivalence margins (1/2, 2) of fold-change, it was found that, of the total 12 comparisons involving 3 lots and 4 serotypes, one comparison of lot1 vs lot2 for serotype 2 had GMT ratio not contained within the margins. The 2-sided 95% CI upper bound of 2.188 exceeded the 2-fold change. In the log10 scale of titer, the observed confidence upper limit of 0.340 on log10titer difference exceeded 0.301, the pre-specified limit which is log10 of 2-fold difference (Table 16).

7.4 Conclusions

1. Overall, the applicant's results showed that the CYD dengue vaccine reduced the VCD incidences in the post-dose 3 period and in the whole Active Phase period. The primary efficacy objective was satisfied.

2. In the lot-to-lot consistency of 3 manufacturing lots, which involved a total of 12 comparisons with 3 lot-pairs and 4 serotypes, the consistency criterion was satisfied except for one comparison of Lot1 vs Lot2 for serotype 2 where the GMT ratio was not contained within pre-specified equivalence margins (1/2,2), and the 2-sided 95% CI upper bound of GMT ratio was

2.188 exceeding 2-fold change. In the log10 scale of titer, the observed confidence upper limit of 0.340 on log10titer difference exceeded 0.301, the pre-specified limit which is log10 of 2-fold difference.

3. The CYD dengue vaccine induced post-dose 3 immune response which showed long-term persistence of seropositivity.

4. The studies from which the adults were selected for immunogenicity bridging with CYD14/15 did not have design pre-specifications and sample size adequacy to enable the type of statistical comparison needed. The proposed immuno-bridging was post-hoc and the results are difficult to interpret statistically. The comparison can only be viewed as descriptive.

8. Integrated Overview of Safety

Deferred to Safety Review by Dr. Huang.

9. Additional Statistical Issues

NA

10. Conclusions

10.1 Statistical Issues and Collective Evidence

Studies CYD14 and CYD15 each included tests of the null hypothesis H_0: VE $\leq$ 25% against the alternative hypothesis H_1: VE > 25%. The pre-specified study success criteria required the lower bound of the 2-sided 95% CI for VE to exceed 25%. This criterion was met in both studies. The studies were powered for overall VE of any serotype, not for individual VEs by serotype.

The submission included immunogenicity bridging of the pivotal efficacy subjects to adult subjects (18-45 years old) in order to extrapolate efficacy for adults. The adults, although dengue seropositive at baseline, were chosen post-hoc from non-pivotal studies that did not have design pre-specifications and adequacy of sample sizes to enable the type of immunogenicity comparisons needed for bridging, thus rendering the comparison inadequate to draw firm conclusions. At the Vaccines and Related Biological Products Advisory Committee (VRBPAC) (March 7, 2019), reservations were expressed about the bridging studies. The Committee voted that efficacy had been demonstrated in individuals 9 through 16 years of age but did not recommend extending the indication to adults based on the bridging studies.

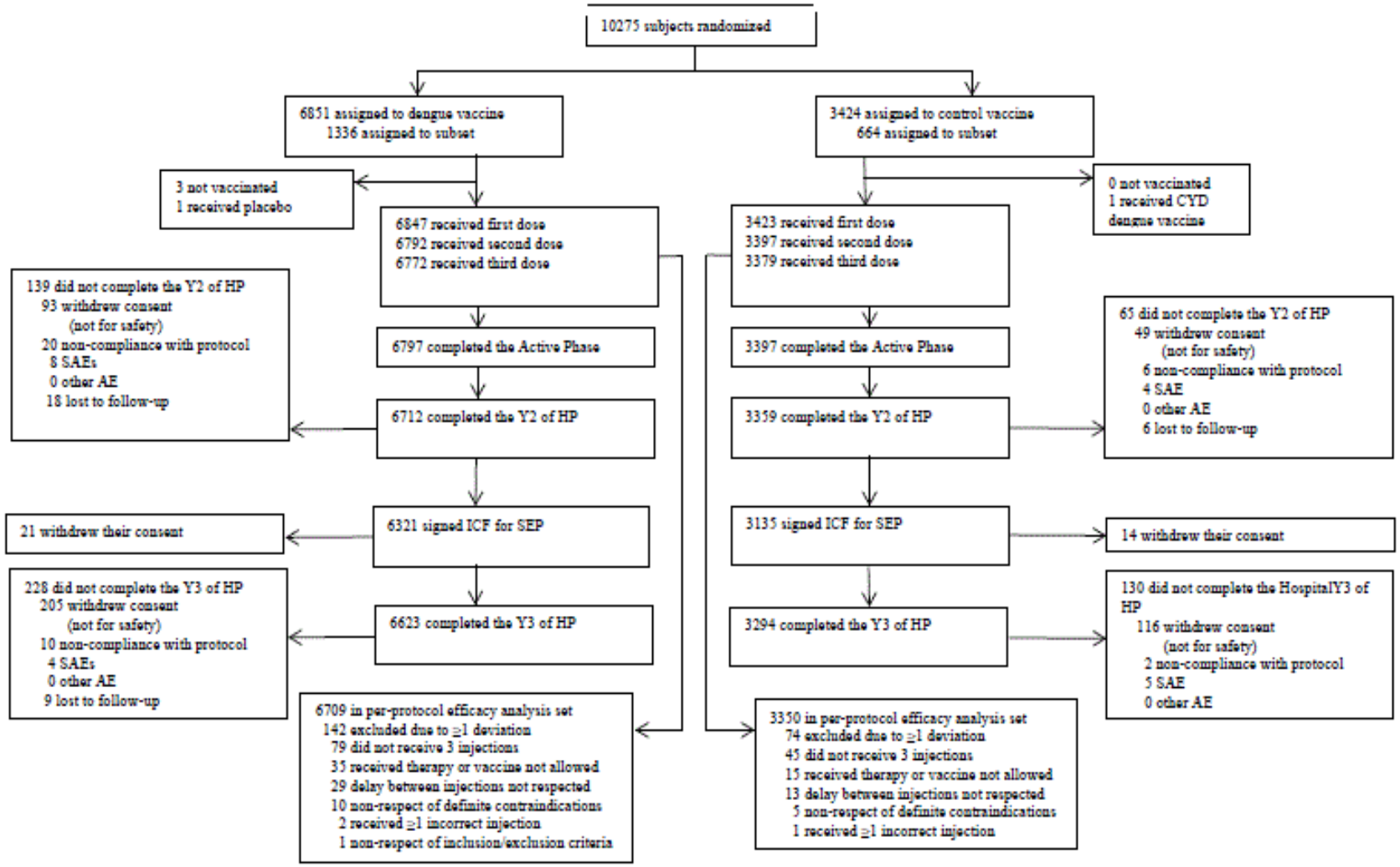
10.2 Conclusions and Recommendations

Statistical analyses support the efficacy and long-term persistence of seropositivity among CYD vaccinees.

The post-hoc immuno-bridging and the issue of consistency of 3 manufacturing lots where one of the 12 comparisons (3 lot-pairs × 4 serotypes) missed the consistency criterion are deferred to reviewers of appropriate disciplines.

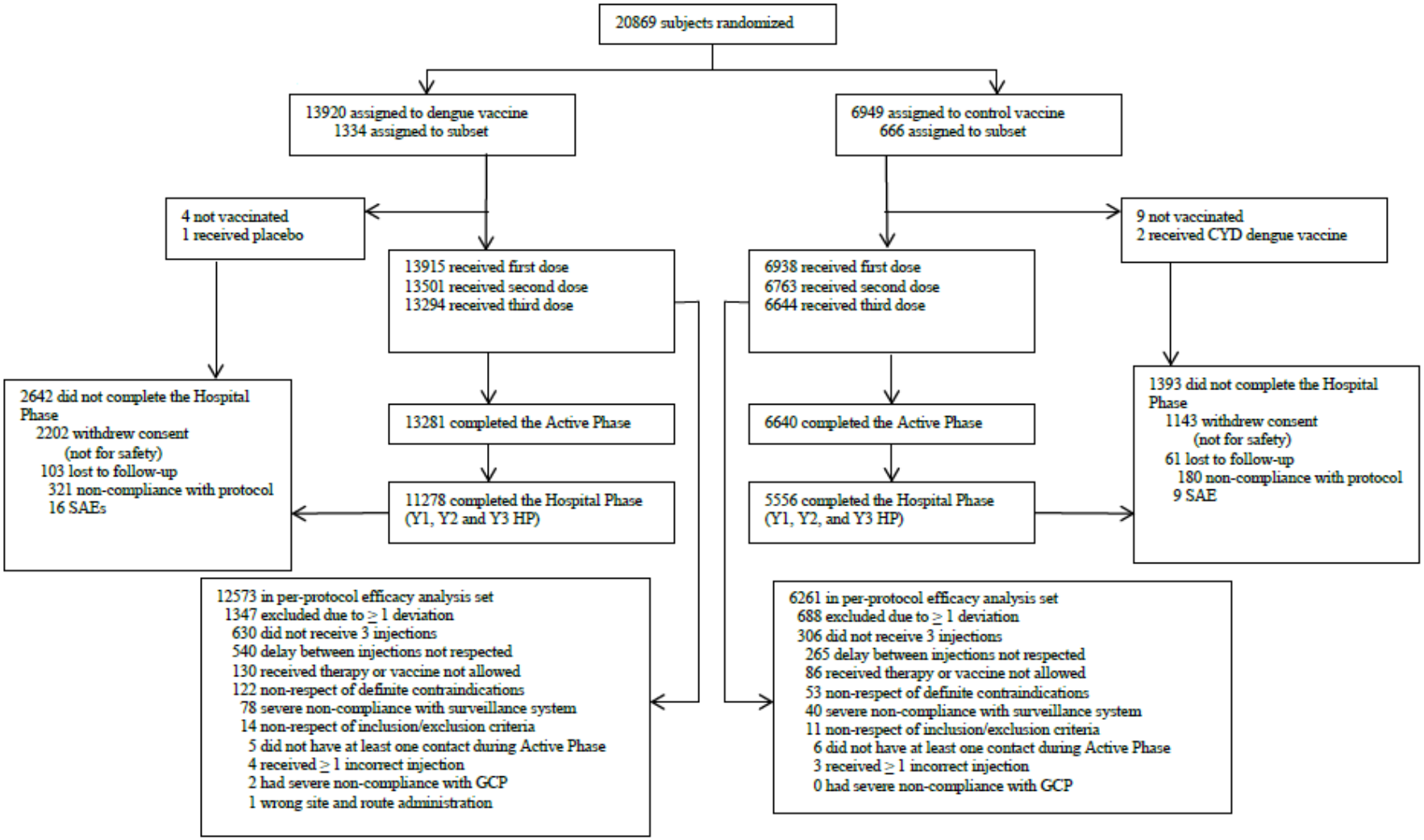
APPENDIX 1

Disposition of subjects CYD14



Source: CSR CYD14, Figure 4.1, page 173 of 1568

Disposition of subjects CYD15



Source: CSR CYD15, Figure 4.1, page 181 of 1622