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Priority Review	Yes
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Review Completion Date / Stamped Date	
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Applicant	Sanofi Pasteur, Inc.
Established Name	Dengue Tetravalent Vaccine (Live, Attenuated)
Trade Name	DENGIVAXIA
Pharmacologic Class	Vaccine
Formulation(s), including Adjuvants, etc	Live, attenuated, chimeric dengue virus (serotypes 1, 2, 3 and 4)
Dosage Form(s) and Route(s) of Administration	Suspension for injection (0.5 mL) supplied as a lyophilized powder to be reconstituted with the supplied diluent; subcutaneous injection
Dosing Regimen	The 3-dose immunization series consists of a 0.5 mL subcutaneous injection administered at 6- month intervals (Month 0, 6, and 12)
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 in individuals 9 through 16 years of age with laboratory- confirmed previous dengue infection and living in endemic areas.

Table of Contents

Glossary	4
1. Executive Summary	5
2. Clinical and Regulatory Background.....	7
2.1 Disease or Health-Related Condition(s) Studied	7
2.2 Currently Available, Pharmacologically Unrelated Treatment(s)/Intervention(s) for the Proposed Indication(s)	7
2.4 Previous Human Experience with the Product (Including Foreign Experience)	7
2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission	8
2.6 Other Relevant Background Information	8
3. Submission Quality and Good Clinical Practices	8
3.1 Submission Quality and Completeness	8
3.2 Compliance With Good Clinical Practices And Data Integrity	8
4. Significant Efficacy/Safety Issues Related to Other Review Disciplines.....	8
4.1 Chemistry, Manufacturing, and Controls	8
4.2 Assay Validation	8
4.3 Nonclinical Pharmacology/Toxicology	8
4.4 Clinical Pharmacology	8
4.5 Clinical	9
4.6 Pharmacovigilance	9
5. Sources of Clinical Data and Other Information Considered in the Review	9
5.1 Review Strategy	9
5.2 BLA/IND Documents That Serve as the Basis for the Statistical Review	9
5.3 Table of Studies/Clinical Trials.....	9
5.4 Consultations	12
5.4.1 Advisory Committee Meeting (if applicable).....	12
5.4.2 External Consults/Collaborations (if applicable)	12
5.5 Literature Reviewed (if applicable).....	12
6. Discussion of Individual Studies/Clinical Trials	12
6.1 Trial #1: CYD14.....	12
6.1.1 Safety Objectives (Primary, Secondary, etc).....	12
6.1.2 Design Overview.....	12
6.1.3 Population	13
6.1.4 Study Treatments or Agents Mandated by the Protocol.....	13
6.1.6 Sites and Centers	13
6.1.7 Surveillance/Monitoring.....	13
6.1.8 Endpoints and Criteria for Study Success	13
6.1.9 Statistical Considerations & Statistical Analysis Plan	14
6.1.10 Study Population and Disposition	14
6.1.11 Efficacy Analyses.....	14
6.1.12 Safety Analyses	14
6.2 Trial #2: CYD15.....	17
6.2.1 Safety Objectives (Primary, Secondary, etc.).....	17
6.2.2 Design Overview.....	17
6.2.3 Population	18
6.2.4 Study Treatments or Agents Mandated by the Protocol.....	18

6.2.6 Sites and Centers	18
6.2.7 Surveillance/Monitoring.....	18
6.2.8 Endpoints and Criteria for Study Success	18
6.2.9 Statistical Considerations & Statistical Analysis Plan	18
6.2.10 Study Population and Disposition	18
6.2.11 Efficacy Analyses.....	18
6.2.12 Safety Analyses	18
6.3 Trial #3: CYD23.....	21
6.3.1 Objectives (Primary, Secondary, etc.).....	21
6.3.2 Design Overview.....	21
6.3.3 Population	21
6.3.4 Study Treatments or Agents Mandated by the Protocol.....	21
6.3.6 Sites and Centers	21
6.3.7 Surveillance/Monitoring.....	22
6.3.8 Endpoints and Criteria for Study Success	22
6.3.9 Statistical Considerations & Statistical Analysis Plan	22
6.3.10 Study Population and Disposition	22
6.3.11 Efficacy Analyses.....	22
6.3.12 Safety Analyses	22
7. Integrated Overview of Efficacy.....	25
8. Integrated Overview of Safety	25
8.1 Safety Assessment Methods	25
8.2 Safety Database	26
8.2.1 Studies/Clinical Trials Used to Evaluate Safety	26
8.2.2 Overall Exposure, Demographics of Pooled Safety Populations	26
8.3 Caveats Introduced by Pooling of Data Across Studies/Clinical Trials	26
8.4 Safety Results	27
8.4.1 Deaths.....	30
8.4.2 Nonfatal Serious Adverse Events.....	30
8.4.3 Study Dropouts/Discontinuations.....	30
8.4.4 Common Adverse Events.....	31
8.4.5 Clinical Test Results.....	31
8.4.6 Systemic Adverse Events	31
8.4.7 Local Reactogenicity	31
8.4.8 Adverse Events of Special Interest.....	31
8.5 Additional Safety Evaluations.....	31
8.5.1 Dose Dependency for Adverse Events	35
8.5.2 Time Dependency for Adverse Events.....	35
8.5.3 Product-Demographic Interactions.....	35
8.5.4 Product-Disease Interactions	35
8.5.5 Product-Product Interactions	36
8.5.6 Human Carcinogenicity.....	36
8.5.8 Immunogenicity (Safety).....	36
8.6 Safety Conclusions	36
10. Conclusions.....	36

GLOSSARY

Abbreviation/Term	Definition
AE	Adverse event
AESI	Adverse event of special interest
BIMO	Clinical and bioresearch and monitoring
CCID ₅₀	Cell-culture infectious dose 50%
CI	Confidence Interval
CMC	Chemistry, manufacturing, and controls
CYD	Chimera yellow fever dengue
IDMC	Independent data monitoring committee
ISS	Integrated summary of safety
MedDRA	Medical dictionary for regulatory activities
NaCl	Sodium chloride
NS1	Non-structural protein 1
PRNT	Plaque reduction neutralization test
PT	Preferred term
RR	Relative risk
SAE	Serious adverse event
SEP	Surveillance expansion phase
SOC	System organ class
SVCD	Severe virologically-confirmed dengue
VCD	Virologically-confirmed dengue
WHO	World Health Organization

1. EXECUTIVE SUMMARY

Sanofi Pasteur submitted the original Biologics License Application (BLA 125682) for CYD Dengue Vaccine (Dengvaxia). CYD dengue vaccine is a tetravalent, live attenuated viral vaccine indicated for active immunization for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in individuals 9 through 16 years of age with laboratory-confirmed previous dengue infection and living in endemic areas.

As no immunological correlate of protection was established, the efficacy of the CYD dengue vaccine, compared to placebo, has been assessed in endemic areas in one proof of concept Phase IIb monocenter study (CYD23 conducted in Thailand in children 4 to 11 years) and two large-scale Phase III studies performed in 10 countries of southeast Asia Pacific (CYD14 in children and adolescent aged 2 to 14 years) and Latin America (CYD15 in children and adolescent aged 9 to 16 years). Clinical efficacy and immunogenicity are discussed in Dr. Mridul Chowdhury's statistical review memo. This memo covers the review of safety data only.

Safety

For Study CYD14, the safety profile over the active phase (day 0 to 13 months post dose 3) was consistent with the profile observed in other studies with no safety signal identified. Reactogenicity, solicited injection site or systemic reactions, unsolicited AEs, and SAEs were reported with similar frequencies in the CYD vaccine and placebo groups. Only 2 SAEs related to trial products were reported during the active phase, one in each group. Five deaths, 4 in the CYD vaccine group and 1 in the control group, were reported during the active phase. A total of six deaths, 3 in each group, were reported during the 3-year hospital/SEP phase (13 months post dose 3 to 48 months post dose 3). None of these deaths were assessed to be related to study treatment. The risk profile against hospitalized virologically-confirmed dengue (VCD) cases and hospitalized severe virologically-confirmed dengue cases was more favorable in older children than younger children.

For Study CYD15, the safety profile over the active phase was consistent with the profile observed in other studies with no safety signal identified. Reactogenicity, solicited injection site or systemic reactions, unsolicited AEs, and SAEs were reported with similar frequencies in the CYD vaccine or placebo group, with the exception that a slightly higher frequency of subjects reported pain as a solicited injection site reaction in the CYD vaccine group than in the placebo group. Twelve deaths, 6 in each group, all unrelated, were reported during the active phase. Twenty-seven deaths in the CYD vaccine group and 17 deaths in the placebo group, all unrelated, were reported during the hospital/SEP phase.

For Study CYD23, the safety profile over the active phase was also consistent with the profile observed in other studies with no safety signal identified. Reactogenicity, solicited injection site or systemic reactions, unsolicited AEs, and SAEs were reported with similar frequencies in the CYD vaccine or placebo group. Only 1 related SAE of acute febrile

illness was reported in the control group. During the entire study period, five unrelated deaths were reported, 1 in the CYD vaccine group and 4 in the control group.

An integrated analysis of safety (ISS) was performed with safety data collected in seventeen main studies (final vaccine schedule) and six secondary studies (other vaccine schedules). The reactogenicity profile of the CYD dengue vaccine in terms of incidence, severity, and nature of events was generally similar to that reported after injection of placebo, although in adults, the incidence of several clinical safety parameters had higher incidence in the CYD vaccine Group than in the Control Group. Unsolicited non-serious AEs within 28 days were reported in approximately 45% of subjects in all age groups except infants and toddlers in which the incidence was slightly higher (54.7%), and the most frequent system organ class (SOC) was Infections and Infestations. SAEs within 28 days after any injection were reported in approximately 1% of subjects (between 0.6% and 1.8% depending on the age group), and were mainly infections, gastrointestinal disorders or injuries commonly reported in these age groups. Deaths were reported with a similar frequency in both CYD vaccine and Control Groups. No deaths were assessed as related to the study vaccine in any study.

Based on data collected over the first 3 years of long-term follow-up (Hospital/Surveillance Expansion Phase) in Studies CYD14, CYD15 and CYD23/57, results from the pooled analysis showed that there was a decreased risk of hospitalized VCD cases in the CYD vaccine Group, and no evidence of an excess of severe virologically-confirmed dengue (SVCD) cases in the CYD vaccine Group compared to the Control Group in subjects above 9 years of age. In subjects aged below 9 years, there was a trend suggesting an increased risk of hospitalized VCD and SVCD in the CYD vaccine group.

The non-structural protein 1 (NS1) supplemental study investigated the relationship between vaccine safety and baseline dengue serostatus over the long-term follow-up period (follow-up of 60 to 72 months post dose 1) in the 3 efficacy studies, and complemented analyses performed in the immunogenicity subsets which had limited precision. The NS1 supplemental study found that dengue serostatus at baseline likely modified the risk of hospitalized dengue and severe dengue after vaccination. In subjects classified as dengue seropositive (subjects previously exposed to natural dengue infection), a decreased risk against hospitalized and severe dengue over the long-term follow-up period was observed following vaccination in subjects 2-16 years of age and particularly in subjects ≥ 9 years. In subjects classified as dengue seronegative prior to dengue vaccination, an increased risk of dengue hospitalization and SVCD following vaccination was observed in subjects 2-16 years of age.

Please refer to the medical officer's review for more safety details.

Conclusion and recommendations

In conclusion, there were no major safety issues related to solicited and unsolicited adverse events, except that the safety profile against hospitalized VCD and SVCD cases appears to be more favorable in older subjects. The additional exploratory analysis results with NS1 assay indicate that baseline serostatus is reasonably likely a risk modifier for

hospitalized VCD and SVCD. However, given that the NS1 analyses are post-hoc and rely on various assumptions of the complicated statistical model, I consider the NS1 analyses exploratory and supportive in nature. I defer to the medical reviewer regarding the overall acceptability of the NS1 analysis results, as well as the overall safety of the vaccine in individuals 9 to 16 years with laboratory-confirmed previous dengue infection.

2. CLINICAL AND REGULATORY BACKGROUND

The clinical development of this vaccine in the United States was performed under BB-IND 11219, initially sponsored and submitted by Acambis on August 15, 2003 with a transfer of sponsorship in January 2005.

As of December 2017, the clinical development plan of Dengvaxia includes 31 clinical studies, completed (22) or ongoing (9): 5 Phase I, 17 Phase II and 9 Phase III. A total of more than 41,000 subjects have been enrolled in clinical studies including more than 28,500 subjects from 9 months through 60 years of age exposed to at least one injection of the final tetravalent CYD dengue vaccine formulation, regardless of the administration schedule. Among these subjects, 19,204 subjects were aged 9 years through 16 years and received at least one injection of the final formulation of the CYD dengue vaccine, regardless of the schedule.

2.1 Disease or Health-Related Condition(s) Studied

Dengue is an acute, systemic viral infection caused by 4 closely related but antigenically distinct virus serotypes (1, 2, 3, and 4) transmitted primarily by the *Aedes aegypti* mosquito. Dengue is the most common mosquito-borne viral disease in humans, spreading globally during the past 30 years as a result of changes in human ecology. Half of the world's population is now considered at risk of infection by the dengue viruses. Worldwide, an estimated 390 million dengue infections occur every year, of which around 100 million are associated with clinical manifestation of dengue.

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

Up to the end of 2015, the only available prevention of dengue by vector control has proven to be of limited success, very difficult to sustain and costly. As recognized by the World Health Organization (WHO), there is an urgent need to develop a safe and effective vaccine against the four serotypes of dengue virus to protect people in endemic countries.

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

Since the first marketing authorization obtained in Mexico on December 8, 2015 Dengvaxia has been licensed in 20 countries in total. However due to a 1-year temporary suspension for the license in the Philippines, as of end June 2018 the vaccine is registered in 19 countries (Argentina, Australia, Bangladesh, Bolivia, Brazil, Cambodia, Costa Rica, El Salvador, Guatemala, Honduras, Indonesia, Malaysia, Myanmar, Mexico, Paraguay, Peru, Singapore, Thailand, and Venezuela). This suspension, dated January 3, 2018, has been justified by the Philippines FDA by an alleged failure to comply with post-

marketing requirement planned dates and was not linked to the product profile. The product has been launched (public or private market) in 11 countries since February 2016: in the Philippines, Brazil, Mexico, El Salvador, Costa-Rica, Guatemala, Paraguay, Peru, Indonesia, Singapore and Thailand.

Cumulative post-approval exposure to CYD Dengue vaccine (from 01 December 2015 to 30 November 2017) was estimated to be 2,896,468 doses. Assuming that patients may have received between 1 and 3 doses in accordance with the recommended schedule, the estimated cumulative number of patients who received CYD Dengue vaccine is between 965,489 and 2,896,468.

2.5 Summary of Pre- and Post-submission Regulatory Activity Related to the Submission
Please refer to the medical officer's review.

2.6 Other Relevant Background Information

Not applicable.

3. SUBMISSION QUALITY AND GOOD CLINICAL PRACTICES

Please refer to the medical and bioresearch monitoring (BIMO) reviews.

3.1 Submission Quality and Completeness

Submission quality is acceptable. The applicant responded to all information requests sent by the agency.

3.2 Compliance With Good Clinical Practices And Data Integrity

Please refer to the BIMO reviews.

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

Please refer to the reviews of the corresponding discipline reviewers.

4.1 Chemistry, Manufacturing, and Controls

Please refer to the CMC review.

4.2 Assay Validation

Please refer to the CMC/bioassay reviews.

4.3 Nonclinical Pharmacology/Toxicology

Not applicable.

4.4 Clinical Pharmacology

Not applicable.

4.5 Clinical

Please refer to the medical officer's review.

4.6 Pharmacovigilance

Please refer to the pharmacovigilance review.

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

5.1 Review Strategy

Safety Reviews for individual Studies CYD14, CYD15, and CYD23 are performed for all subjects in the safety analysis set regardless of age in Section 6. ISS is presented in Section 8. The ISS analyses were performed by different age groups. The review for ISS focuses on the safety data in the 9- 17 years group in line with the indication the applicant is seeking.

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

This review is based on the applicant's original BLA submission (STN125682/0) dated August 31, 2018 and subsequent amendments (Amendments #4, #28, #38, and #42) to the original submission, primarily Modules 2 and 5 in the Electronic document Room (EDR).

5.3 Table of Studies/Clinical Trials

Table 1 provides a description of the key studies (CYD14, CYD15, and CYD23/57) included in the BLA.

Table 1. Listing of Key Clinical Studies

Study Identifier (Country; Endemic/non-endemic) Age	Main Objective	Study Design	Test Products; Dosage Regimen	Number of Subjects	Study Status
CYD23 (Thailand; Endemic) 4–11 years	<ul style="list-style-type: none"> - Vaccine efficacy against virologically confirmed dengue cases. - Descriptive dengue humoral immune response, before and after each injection and one year after the 3rd injection, in a subset of subjects. - Safety throughout the trial and descriptive reactogenicity (injection site and systemic), after each injection, in a subset of subjects. - Vaccine viremia, after the 1st and 2nd injections, in a subset of subjects. 	Phase IIb, randomized, controlled, blind-observer, monocenter trial.	CYD Dengue Vaccine (~5 log₁₀CCID₅₀/serotype 1, 2, 3, 4) Group 1: CYD dengue vaccine - 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.	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	Completed
CYD57 (Thailand; Endemic) 4–11 years at enrollment in CYD23	<ul style="list-style-type: none"> - 4-year post-injection 3 safety follow-up of subjects previously enrolled in CYD23. - Detection and characterization of hospitalized dengue cases. - Evaluation of occurrences of related (linked to CYD dengue vaccine received in CYD23) and fatal SAEs. 	Monocenter, safety follow-up study of CYD23.	No vaccine administration.	Included: 3203 Group 1: 2131 Group 2: 1072 (subjects included in CYD23)	Completed
CYD14 (Indonesia, Malaysia, Thailand, the Philippines, Vietnam; Endemic) 2–14 years	<ul style="list-style-type: none"> - Vaccine efficacy against virologically confirmed dengue cases. - Safety throughout the trial and descriptive reactogenicity (injection site and systemic) after each injection, in a subset of subjects. - Descriptive dengue humoral immune response, after the 2nd and 3rd injection, in a subset of subjects. - 5-year post-injection 3 follow-up/Surveillance Expansion Phase (SEP): safety, detection of confirmed hospitalized dengue cases and antibody persistence in a subset of subjects. - Vaccine efficacy against virologically-confirmed dengue cases, hospitalized cases and severe cases during the SEP 	Phase III, randomized, placebo-controlled, blind-observer, multicenter trial.	CYD Dengue Vaccine (~5 log₁₀CCID₅₀/serotype 1, 2, 3, 4) Group 1: CYD dengue vaccine at D0, M6 and M12. Group 2: Placebo (NaCl 0.9%) at D0, M6 and M12.	Randomized: 10,275 - Group 1: 6851 - Group 2: 3424	Ongoing

Table 1. Listing of Key Clinical Studies (Cont'd)

Study Identifier (Country; Endemic/non- endemic) Age	Main Objective	Study Design	Test Products; Dosage Regimen	Number of Subjects	Study Status
CYD15 (Brazil, Colombia, Honduras, Mexico, Puerto Rico; Endemic) 9–16 years	<ul style="list-style-type: none"> - Vaccine efficacy against virologically confirmed dengue cases. - Safety throughout the trial and descriptive reactogenicity (injection site and systemic) after each injection, in a subset of subjects. - Descriptive dengue humoral immune response, after the 2nd and 3rd injection, in a subset of subjects. - 5-year post-injection 3 follow-up/SEP: safety, detection of confirmed hospitalized dengue cases and antibody persistence in a subset of subjects. - Vaccine efficacy against virologically-confirmed dengue cases, hospitalized cases and severe cases during the SEP 	Phase III, randomized, placebo-controlled, blind-observer, multicenter trial.	CYD Dengue Vaccine (~5 log₁₀CCID₅₀/serotype 1, 2, 3, 4) Group 1: CYD dengue vaccine at D0, M6 and M12. Group 2: Placebo (NaCl 0.9%) at D0, M6 and M12.	Randomized: 20,869 - Group 1: 13,920 - Group 2: 6949	Ongoing

Source: Adapted from Table 1 in Module 5.2 Tabular Listing of all Clinical Studies.

5.4 Consultations

Not applicable.

5.4.1 Advisory Committee Meeting (if applicable)

An advisory committee meeting was held on March 7, 2019 to discuss and make recommendations on the safety and effectiveness of Dengvaxia. The results of the committee meeting related to safety are summarized below:

- Seven committee members voted Yes and seven voted No to the question “Are the available data adequate to support the safety of Dengvaxia when administered to persons 9 through 45 years of age with laboratory-confirmed previous dengue infection and living in endemic areas?”
- Ten committee members voted Yes and four voted No to the question “Are the available data adequate to support the safety of Dengvaxia when administered to persons 9 through <17 years of age with laboratory-confirmed previous dengue infection and living in endemic areas?”

5.4.2 External Consults/Collaborations (if applicable)

Not applicable.

5.5 Literature Reviewed (if applicable)

Not applicable.

6. DISCUSSION OF INDIVIDUAL STUDIES/CLINICAL TRIALS

Studies CYD14, CYD15 and CYD23 (in order) are discussed in the following subsections.

6.1 Trial #1: CYD14

This protocol was entitled “*Efficacy and safety of a novel tetravalent dengue vaccine in healthy children aged 2 to 14 years in Asia.*”

6.1.1 Safety Objectives (Primary, Secondary, etc)

- To describe the occurrence of SAEs, including serious adverse events of special interest (AESIs), in all subjects throughout the trial period.
- To describe the occurrence of hospitalized virologically-confirmed dengue cases and the occurrence of severe (clinically-severe or as per WHO criteria) virologically-confirmed dengue cases, throughout the Surveillance Expansion period (SEP) and throughout the trial (from Day 0 until the end of the trial).

6.1.2 Design Overview

This was a Phase 3 efficacy trial with a randomized, observer-blind, placebo-controlled, multi-center design in 5 different countries. Children aged 2 to 14 years received 3 injections at 0, 6, and 12 months and were randomized in a 2:1 ratio so that 6853 subjects were to receive CYD dengue vaccine and 3426 were to receive placebo. A subset of

subjects from each country was evaluated for immunogenicity and reactogenicity. The study consists of a 2-year active phase (from Day 0 to 13 months post dose 3), and an approximately 47-month hospital phase after 3 doses of vaccination. The hospital phase was later modified to the SEP phase for active dengue case detection.

6.1.3 Population

All subjects in this study were 2 through 14 years of age.

6.1.4 Study Treatments or Agents Mandated by the Protocol

Subjects were to receive either 3 doses of the investigational product, CYD dengue vaccine, or placebo as control product at Months 0, 6, and 12. Each 0.5 mL dose of reconstituted vaccine contained 4.5-6 log₁₀ cell-culture infectious dose 50% (CCID₅₀) of each live, attenuated, recombinant, dengue serotypes 1, 2, 3, and 4 viruses. The placebo is NaCl 0.9%.

6.1.6 Sites and Centers

The study was conducted in 11 sites in 5 countries (Indonesia, Malaysia, Thailand, the Philippines, and Vietnam).

6.1.7 Surveillance/Monitoring

Please refer to the medical officer's review.

6.1.8 Endpoints and Criteria for Study Success

Please refer to the statistical review of clinical efficacy data for efficacy and immunogenicity endpoints, and study success criteria.

Safety Endpoints

The primary safety endpoints included:

- Occurrence of SAEs, including serious AESIs, in all subjects throughout the entire study.
- Occurrence of hospitalized VCD cases and occurrence of severe (clinically-severe or as per WHO criteria) confirmed dengue cases, occurring during the SEP and during the trial.
- Occurrence, nature, duration, intensity, action taken, and relationship to vaccination of any unsolicited systemic AEs reported in the 30 minutes after each dose.
- Occurrence, time to onset, number of days of occurrence, action taken, and intensity of solicited, injection site reactions occurring up to 7 days after each dose.
- Occurrence, nature, time to onset, duration, intensity, action taken, and relationship to vaccination of unsolicited AEs up to 28 days after each dose.
- Occurrence, nature, time to onset, duration, intensity, action taken, and relationship to vaccination of non-serious AESIs occurring up to 7 days after each dose.

6.1.9 Statistical Considerations & Statistical Analysis Plan

Safety Analysis

SAEs were described by MedDRA preferred term, outcome and relationship to vaccination. The 95% CIs for percentages were calculated using the exact binomial distribution (Clopper-Pearson method). Serious AESIs were described using the same method. The number of subjects with serious dengue disease was summarized by country and time of onset.

Hospitalized and severe VCD cases were described in the SEP and throughout the trial in each treatment arm, overall and yearly. Incidence, relative risk and their 95% CIs were computed.

6.1.10 Study Population and Disposition

A total of 10,275 subjects were randomized (3 subjects were randomized twice), of which 6851 in the CYD vaccine group and 3424 in the control group. Please refer to the statistical review memo for clinical efficacy data for detailed study population and disposition information.

6.1.11 Efficacy Analyses

Please refer to the statistical review of clinical efficacy and immunogenicity data.

6.1.12 Safety Analyses

All subjects were assessed for safety (SAEs) and a subset was assessed for reactogenicity solicited reaction and unsolicited non-serious AEs. Table 2 summarizes the overview of reactogenicity data up to 28 days after any injections, and SAEs.

Table 2. Safety overview after any injections – safety analysis set (CYD14)

	CYD Vaccine Group (N=6848)			Control Group (N=3424)		
Subjects experiencing at least one:	n/M	%	(95% CI)	n/M	%	(95% CI)
Reactogenicity subset						
Within 28 days after any vaccine injections						
Immediate unsolicited non-serious AE	0/1334	0.0	(0.0; 0.3)	0/663	0.0	(0.0; 0.6)
Immediate unsolicited non-serious AR	0/1334	0.0	(0.0; 0.3)	0/663	0.0	(0.0; 0.6)
Solicited reaction	896/1332	67.3	(64.7; 69.8)	423/663	63.8	(60.0; 67.5)
Solicited injection site reaction	633/1332	47.5	(44.8; 50.2)	285/663	43.0	(39.2; 46.9)
Solicited systemic reaction	760/1332	57.1	(54.3; 59.7)	367/663	55.4	(51.5; 59.2)
Unsolicited non-serious AE	489/1334	36.7	(34.1; 39.3)	268/663	40.4	(36.7; 44.3)
Unsolicited non-serious AR	19/1334	1.4	(0.9; 2.2)	6/663	0.9	(0.3; 2.0)
Unsolicited non-serious injection site AR	9/1334	0.7	(0.3; 1.3)	2/663	0.3	(0.0; 1.1)
Unsolicited non-serious systemic AE	489/1334	36.7	(34.1; 39.3)	268/663	40.4	(36.7; 44.3)
Unsolicited non-serious systemic AR	10/1334	0.7	(0.4; 1.4)	4/663	0.6	(0.2; 1.5)
All subjects						
Within 28 days after any vaccine injections						
AE leading to discontinuation*	1/6848	<0.1	(0.0; 0.1)	0/3424	0.0	(0.0; 0.1)
Immediate SAE	1/6848	<0.1	(0.0; 0.1)	0/3424	0.0	(0.0; 0.1)
SAE	54/6848	0.8	(0.6; 1.0)	33/3424	1.0	(0.7; 1.4)
Death	1/6848	<0.1	(0.0; 0.1)	0/3424	0.0	(0.0; 0.1)
During the active period						
AE leading to discontinuation*	4/6848	<0.1	(0.0; 0.1)	1/3424	<0.1	(0.0; 0.2)
SAE	355/6848	5.2	(4.7; 5.7)	220/3424	6.4	(5.6; 7.3)
Death	4/6848	<0.1	(0.0; 0.1)	1/3424	<0.1	(0.0; 0.2)
During the HP/SEP						
AE leading to discontinuation*	4/6782	<0.1	(0.0; 0.2)	5/3387	0.1	(0.0; 0.3)
SAE	517/6782	7.6	(7.0; 8.3)	294/3387	8.7	(7.8; 9.7)
Death	3/6782	<0.1	(0.0; 0.1)	3/3387	<0.1	(0.0; 0.3)
During the entire study						
AE leading to discontinuation*	8/6848	0.1	(0.1; 0.2)	6/3424	0.2	(0.1; 0.4)
SAE	804/6848	11.7	(11.0; 12.5)	479/3424	14.0	(12.8; 15.2)
Death	7/6848	0.1	(0.0; 0.2)	4/3424	0.1	(0.0; 0.3)

n: number of subjects experiencing the endpoint listed in the first column

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

*Identified in the termination form (at V06, V07, V10, V11, and V12) as SAE or other AE.

Source: Table 7.1 of the Interim Report V4.0 for CYD14.

Reviewer Comments

1. Subject (b) (6) was randomized to the CYD vaccine group. However, this subject received placebo in the 1st injection, and CYD dengue vaccine in the 2nd and 3rd injections. The applicant's safety analyses included this subject in the control group. I consider it more appropriate to include this subject in the CYD

vaccine group after the subject received the CYD dengue vaccine in the safety analyses. Since this subject was not in the reactogenicity subset (hence no reactogenicity data were reported), and there was no SAE reported for this subject, the only impact of misclassifying this subject on the safety analyses is the total number of subjects in each treatment group. The impact on the calculation of AE occurrence is minimal.

- 2. A total of 51 unsolicited non-serious AEs had missing severity information, 31 in the CYD vaccine group and 20 in the control group. All these AEs were assessed as not related to the investigational product. I shared the list of these AEs with the clinical reviewer and defer to clinical reviewer whether any AEs should be queried for additional information.*
- 3. Overall, the safety profile for the CYD vaccine group appears similar to that of the control group. No systematic pattern was identified.*

Reactogenicity profile of the CYD dengue vaccine was similar to that of placebo. Solicited injection site or systemic reactions, and unsolicited AEs were reported with similar frequencies after injection with CYD dengue vaccine or placebo.

SAE

Overall, a total of 575 subjects experienced 647 SAEs during the active phase: 355 subjects (5.2%) in the CYD vaccine group reporting 402 SAEs and 220 subjects (6.4%) in the control group reporting 245 SAEs. SAEs are reported with similar frequencies in the hospital phase/surveillance expansion period (HP/SEP). A total of 2 SAEs were assessed as related to the investigational products according to the investigator during the active phase: 1 in CYD vaccine group (acute disseminated encephalomyelitis) and 1 in the control group (allergic angioedema). Both related SAEs led to discontinuation of vaccination. All SAEs occurred during the HP/SEP were reported as unrelated to vaccination.

Clinically-severe VCD Cases (IDMC Assessment)

A total of 32 SVCD cases were observed in the 25-month active phase, 18 of which were post Dose 3. There were 12 cases in the 2 to 5 years age group (7 in the CYD vaccine group and 5 in the control group), 17 cases in the 6 to 11 years age group (5 in the CYD vaccine group and 12 in the control group), and 3 cases in the 12 to 14 years age group (0 in the CYD vaccine group and 3 in the control group).

A total of 54 severe cases were reported in the 3-year HP/SEP, of which, 20 cases in the 2 to 5 years age group (18 in the CYD vaccine group and 2 in the control group), 29 cases in the 6 to 11 years age group (18 in the CYD vaccine group and 11 in the control group), and 5 cases in the 12 to 14 years age group (2 in the CYD vaccine group and 3 in the control group).

Reviewer Comments

An increased risk of hospitalized VCD and SVCD in the CYD vaccine group was observed. This has been interpreted by some within the scientific community as a possible indication of an increased risk of dengue hospitalization or severe dengue illness in

individuals who have not been exposed to dengue prior to being vaccinated with CYD dengue vaccine. Since baseline serostatus is only available for a small subset (immunogenicity subset), no conclusive analyses examining this hypothesis can be performed because of the limited number of cases in the subset. Hence, an exploratory analysis utilizing the NS1 assay to impute the baseline serostatus was performed based on the pooled data set from Studies CYD14, CYD15 and CYD23/57. This exploratory analysis is reviewed in Section 8.5.

6.1.12.3 Deaths

Overall, 5 deaths (4 in the CYD vaccine group and 1 in the control group) were reported during the active phase, and 6 deaths were reported during the 3-year HP/SEP (3 in the CYD vaccine group and 3 in the control group). All deaths reported were unrelated to the investigational products.

6.1.12.7 Dropouts and/or Discontinuations

Overall, a total of 11 subjects did not complete the vaccination period due to SAEs: 6 subjects in the CYD vaccine group and 5 subjects in the control group. Eight subjects did not complete the vaccination period due to other AEs, 4 subjects in each of the CYD vaccine and control groups. Five subjects presented SAE that led to discontinuation or early termination from the study during the Active Phase (up to 13 months after the third vaccination): 4 subjects in the CYD vaccine Group and 1 subject in the Control Group. As of Visit10, i.e., 36 months after the last vaccination, 12 subjects were reported to have discontinued or terminated due to an SAE: 8 subjects in the CYD vaccine group and 4 subjects in the control group. As of Visit 11, i.e., 48 months after the last vaccination, 2 additional subjects discontinued due to an SAE, both in the Control Group.

6.2 Trial #2: CYD15

This protocol was entitled “*Efficacy and Safety of a Novel Tetravalent Dengue Vaccine in Healthy Children and Adolescent Aged 9 to 16 Years in Latin America.*”

6.2.1 Safety Objectives (Primary, Secondary, etc.)

The safety objectives for Study CYD15 were the same as those for Study CYD14. Please refer to Section 6.1.1.

6.2.2 Design Overview

CYD15 was a randomized, placebo-controlled, observer-blind, multicenter, Phase III trial in 5 countries, involving 20,875 subjects. Children and adolescents aged 9 to 16 years were randomized 2:1 to receive 3 injections (at 0, 6, and 12 months), so that 13,917 subjects were to receive CYD dengue vaccine and 6958 subjects were to receive placebo. Immunogenicity and reactogenicity were assessed in a subset of 2000 subjects (1334 in the CYD vaccine group and 666 in the control group). The study consists of a 2-year active phase, and an approximately 47-month hospital phase after 3 doses of vaccination. The hospital phase was later modified to the SEP phase for active dengue case detection.

6.2.3 Population

All subjects in this study were ≥ 9 and ≤ 16 years of age.

6.2.4 Study Treatments or Agents Mandated by the Protocol

Same as Study CYD14. Please refer to Section 6.1.4.

6.2.6 Sites and Centers

The study was conducted at 22 sites across Brazil, Colombia, Honduras, Mexico, and Puerto Rico.

6.2.7 Surveillance/Monitoring

Please refer to the medical officer's review.

6.2.8 Endpoints and Criteria for Study Success

Please refer to the statistical review of clinical efficacy data for efficacy and immunogenicity endpoints, and study success criteria. The safety endpoints for Study CYD15 are the same as those for Study CYD14. Please refer to Section 6.1.8.

6.2.9 Statistical Considerations & Statistical Analysis Plan

Safety analyses were similar to those in Study CYD14. Please refer to Section 6.1.9.

6.2.10 Study Population and Disposition

A total of 20,869 subjects were randomized, 13,920 to the CYD vaccine group and 6,949 to the control group. The planned number of subjects in the overall population, $n=20,875$, was not achieved because 6 subjects were randomized twice or three times. Please refer to the statistical review memo for clinical efficacy data for detailed study population and disposition information.

6.2.11 Efficacy Analyses

Please refer to the statistical review of clinical efficacy and immunogenicity data.

6.2.12 Safety Analyses

All subjects were assessed for safety (SAEs) and a subset was assessed for reactogenicity, solicited reactions, and unsolicited non-serious AEs. Table 3 summarizes the overview of reactogenicity data up to 28 days after any injections, and SAEs.

Table 3. Safety overview after any injections – safety analysis set (CYD15)

	CYD Vaccine Group (N=13915)			Control Group (N=6939)		
Subjects experiencing at least one:	n/M	%	(95% CI)	n/M	%	(95% CI)
Reactogenicity subset						
Within 28 days after any vaccine injections						
Immediate unsolicited non-serious AE	3/1333	0.2	(0.0; 0.7)	1/664	0.2	(0.0; 0.8)
Immediate unsolicited non-serious AR	1/1333	<0.1	(0.0; 0.4)	1/664	0.2	(0.0; 0.8)
Solicited reaction	994/1328	74.8	(72.4; 77.2)	495/659	75.1	(71.6; 78.4)
Solicited injection site reaction	675/1328	50.8	(48.1; 53.6)	279/658	42.4	(38.6; 46.3)
Solicited systemic reaction	909/1328	68.4	(65.9; 70.9)	458/659	69.5	(65.8; 73.0)
Unsolicited non-serious AE	595/1333	44.6	(41.9; 47.4)	292/664	44.0	(40.2; 47.8)
Unsolicited non-serious AR	16/1333	1.2	(0.7; 1.9)	5/664	0.8	(0.2; 1.7)
Unsolicited non-serious injection site AR	9/1333	0.7	(0.3; 1.3)	3/664	0.5	(0.1; 1.3)
Unsolicited non-serious systemic AE	592/1333	44.4	(41.7; 47.1)	290/664	43.7	(39.9; 47.5)
Unsolicited non-serious systemic AR	7/1333	0.5	(0.2; 1.1)	2/664	0.3	(0.0; 1.1)
All subjects						
Within 28 days after any vaccine injections						
AE leading to discontinuation*	0/13915	0.0	(0.0; 0.0)	0/6939	0.0	(0.0; 0.1)
Immediate SAE	0/13915	0.0	(0.0; 0.0)	0/6939	0.0	(0.0; 0.1)
SAE	82/13915	0.6	(0.5; 0.7)	42/6939	0.6	(0.4; 0.8)
Death	0/13915	0.0	(0.0; 0.0)	0/6939	0.0	(0.0; 0.1)
During the active period						
AE leading to discontinuation*	10/13915	<0.1	(0.0; 0.1)	9/6939	0.1	(0.1; 0.2)
SAE	571/13915	4.1	(3.8; 4.4)	311/6939	4.5	(4.0; 5.0)
Death	6/13915	<0.1	(0.0; 0.1)	6/6939	<0.1	(0.0; 0.2)
During the HP/SEP						
AE leading to discontinuation*	27/13296	0.2	(0.1; 0.3)	18/6644	0.3	(0.2; 0.4)
SAE	1009/13296	7.6	(7.1; 8.1)	518/6644	7.8	(7.2; 8.5)
Death	27/13296	0.2	(0.1; 0.3)	17/6644	0.3	(0.1; 0.4)
During the entire study						
AE leading to discontinuation*	37/13915	0.3	(0.2; 0.4)	27/6939	0.4	(0.3; 0.6)
SAE	1494/13915	10.7	(10.2; 11.3)	790/6939	11.4	(10.6; 12.2)
Death	33/13915	0.2	(0.2; 0.3)	23/6939	0.3	(0.2; 0.5)

n: number of subjects experiencing the endpoint listed in the first column

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

* Identified in the termination form (at V06, V07, V10, V11, and V12) as SAE or other AE.

Source: Table 7.1 of the Interim Report V4.0 for CYD15.

Reviewer Comments

1. Subject (b) (6) was randomized to the control group. However, this subject received placebo in the 1st and 3rd injections, and CYD dengue vaccine in the 2nd injection. The applicant's safety analyses included this subject in the control group. I consider it more appropriate to include this subject in the CYD

- vaccine group after the subject received the CYD dengue vaccine in the safety analyses. Since this subject was not in the reactogenicity subset (hence no reactogenicity data were reported), the only impact of misclassifying this subject on the safety analyses is the total number of subjects in each treatment group. The impact on the calculation of AE occurrence is negligible.*
- 2. A total of 62 unsolicited non-serious AEs had missing severity, 48 in the CYD vaccine group and 14 in the control group. Two of these AEs in the CYD vaccine group (both injection site haematoma) were assessed as related to the investigational product. I shared the list of these AEs with the clinical reviewer and defer to clinical reviewer whether any AEs should be queried for additional information.*
 - 3. Overall, the safety profile for the CYD vaccine group appears similar to that of the control group. No systematic pattern was identified.*

Reactogenicity profile of the CYD dengue vaccine was similar to that of placebo. Solicited injection site or systemic reactions, and unsolicited AEs were reported with similar frequency after injection with CYD dengue vaccine or placebo.

SAE

Overall, a total of 882 subjects reported at least 1 SAE during the active phase: 571 subjects (4.1%) in the CYD vaccine group and 311 subjects (4.1%) in the control group. SAEs are reported with similar frequency (about 2.5%) in the hospital phase/surveillance expansion period (HP/SEP). A total of 4 SAEs were assessed as related to the investigational products according to the investigator during the active phase: 3 in the CYD vaccine group (acute polyneuropathy, asthmatic attack, and allergic urticaria) and 1 in the control group (visual impairment). All SAEs occurring during the HP/SEP were reported as unrelated to vaccination.

Clinically-severe VCD Cases (IDMC Assessment)

During the Active Phase, a total of 60 subjects were hospitalized for a VCD case due to any serotype (17 in the CYD vaccine Group and 43 in the Control Group), and a total of 12 severe cases were observed (1 in the CYD vaccine group and 11 in the control group). During the Hospital Phase/SEP, a total of 58 subjects were hospitalized for a VCD due to any serotype (29 in each of the CYD vaccine group and control group), and a total of 14 SVCD were observed (9 in the CYD vaccine group and 5 in the control group).

6.2.12.3 Deaths

A total of 12 deaths were reported during the active phase, 6 in each group. None was assessed as related to vaccination. A total of 44 deaths were reported during the HP/SEP, 27 in the CYD vaccine group and 17 in the Control group. None was assessed as related to vaccination.

6.2.12.7 Dropouts and/or Discontinuations

During the Active Phase, there were 10 subjects in the CYD vaccine Group (7 for SAE, 3 for Other AE) and 9 in the Control Group (9 for SAE) who terminated the study early due to AE or SAE. During the 3-year Hospital Phase/SEP, a total of 27 subjects in the CYD

vaccine group and 18 subjects in the control group who terminated the study early due to SAE.

6.3 Trial #3: CYD23

This protocol was entitled “*Efficacy and Safety of Dengue Vaccine in Healthy Children Aged 4 to 11 years in Thailand.*”

6.3.1 Objectives (Primary, Secondary, etc.)

Safety Objective

- To evaluate the occurrence of serious adverse events in all subjects throughout the trial period.
- To evaluate the reactogenicity of dengue vaccine in terms of injection site and systemic reactogenicity after each injection in a subgroup of children aged 4 to 11 years at the time of inclusion.

6.3.2 Design Overview

CYD23 was a randomized, observer-blind, controlled, single center, Phase IIb trial in 4002 subjects aged 4 to 11 years in Thailand. There were 3 injections and 2 groups of subjects:

- CYD vaccine group – 2668 subjects received CYD dengue vaccine (100 subjects in Cohort 1 and 2568 in Cohort 2)
- Control group – 1334 subjects received either 1 injection of rabies vaccine and 2 injections of placebo (50 subjects in Cohort 1) or 3 injections of placebo (1284 subjects).

Cohort 2 was approved to enroll after safety data of Cohort 1 were reviewed by an independent data monitoring committee. Subjects were followed for at least 13 months after the third injection so that an adequate number of dengue cases were observed. Beyond this time point, the detection of hospitalized dengue cases up to 5 years after the last injection in addition to fatal and related SAEs were collected in Study CYD57.

6.3.3 Population

All subjects in this study were ≥ 4 and ≤ 11 years of age.

6.3.4 Study Treatments or Agents Mandated by the Protocol

Subjects in the CYD vaccine group received 1 dose of CYD dengue vaccine at Day 0, Day 0+6 months, and Day 0 +12 months; subjects in the control group received 1 dose of rabies vaccine and 2 doses of placebo (Cohort 1), or 3 doses of placebo (Cohort 2) at Day 0, Day 0+6 months, and Day 0 +12 months.

6.3.6 Sites and Centers

The study was conducted in 1 site in Thailand.

6.3.7 Surveillance/Monitoring

Please refer to the medical officer's review.

6.3.8 Endpoints and Criteria for Study Success

Please refer to the statistical review of clinical efficacy data for efficacy and immunogenicity endpoints and study success criteria.

Safety Endpoints

- Occurrence of SAEs up to 6 months after the last injection and related or fatal SAEs from 6 months after the last injection until the end of the trial
- Occurrence of unsolicited AEs reported in the 30 minutes after each vaccination and up to 28 days after each vaccination
- Occurrence of solicited injection site reactions occurring up to 7 days after each vaccination, and solicited systemic reactions occurring up to 14 days after each vaccination

6.3.9 Statistical Considerations & Statistical Analysis Plan

Solicited reactions will be described according to their severity and according to time to onset, number of days of occurrence, action taken, and according to whether they lead to trial discontinuation. Unsolicited AEs will be described by MedDRA System Organ Class and preferred term definition according to their relationship, severity, time to onset, and duration. SAEs will be described by MedDRA preferred term, outcome and relationship to vaccination throughout the trial (including the 6-month follow-up).

6.3.10 Study Population and Disposition

A total of 4002 subjects were randomized, 2669 to the CYD vaccine group and 1333 to the control group.

6.3.11 Efficacy Analyses

Please refer to the statistical review of clinical efficacy and immunogenicity data.

6.3.12 Safety Analyses

Table 4 presents the safety overview after any injections for all subjects in Cohorts 1 and 2.

Table 4. Safety overview after any injections – Cohorts 1 & 2 - Reactogenicity Subset (CYD23)

	CYD Vaccine Group (N=697)			Control Group (N=350)		
Subjects experiencing at least one:	n/M	%	(95% CI)	n/M	%	(95% CI)
Immediate unsolicited AE	0/697	0.0	(0.0; 0.5)	0/350	0.0	(0.0; 1.0)
Immediate unsolicited AR	0/697	0.0	(0.0; 0.5)	0/350	0.0	(0.0; 1.0)
Solicited reaction	578/692	83.5	(80.5; 86.2)	281/350	80.3	(75.7; 84.3)
Grade 3 solicited reaction	33/692	4.8	(3.3; 6.6)	27/350	7.7	(5.1; 11.0)
Solicited injection site reaction	426/692	61.6	(57.8; 65.2)	218/349	62.5	(57.2; 67.6)
Grade 3 injection site reaction	3/692	0.4	(0.1; 1.3)	1/349	0.3	(0.0; 1.6)
Solicited systemic reaction	538/692	77.7	(74.5; 80.8)	261/350	74.6	(69.7; 79.1)
Grade 3 systemic reaction	32/692	4.6	(3.2; 6.5)	26/350	7.4	(4.9; 10.7)
Unsolicited AE	317/697	45.5	(41.7; 49.3)	162/350	46.3	(41.0; 51.7)
Unsolicited AR	10/697	1.4	(0.7; 2.6)	1/350	0.3	(0.0; 1.6)
Unsolicited non-serious AE	308/697	44.2	(40.5; 48.0)	154/350	44.0	(38.7; 49.4)
Grade 3 unsolicited non-serious AE	21/697	3.0	(1.9; 4.6)	14/350	4.0	(2.2; 6.6)
Unsolicited non-serious AR	10/697	1.4	(0.7; 2.6)	1/350	0.3	(0.0; 1.6)
Grade 3 unsolicited non-serious AR	1/697	0.1	(0.0; 0.8)	0/350	0.0	(0.0; 1.0)
Unsolicited non-serious injection site AR	7/697	1.0	(0.4; 2.1)	1/350	0.3	(0.0; 1.6)
Unsolicited non-serious systemic AE	306/697	43.9	(40.2; 47.7)	154/350	44.0	(38.7; 49.4)
Unsolicited non-serious systemic AR	3/697	0.4	(0.1; 1.3)	0/350	0.0	(0.0; 1.0)
AE leading to study discontinuation *	0/697	0.0	(0.0; 0.5)	0/350	0.0	(0.0; 1.0)
SAE until 6 months after the last injection	90/697	12.9	(10.5; 15.6)	44/350	12.6	(9.3; 16.5)
SAE from 6 months after the last injection†	0/697	0.0	(0.0; 0.5)	0/350	0.0	(0.0; 1.0)
Death	0/697	0.0	(0.0; 0.5)	0/350	0.0	(0.0; 1.0)

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

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

* Identified in the termination form as SAE or other AE.

† SAEs collected up to the end of the Active Phase for the first analysis and all through the trial for the final analysis.

Source: Table 6.1 of the Final Report V2.0 for CYD23.

Reviewer comments:

- Two subjects ((b) (6)), were randomized to the control group, but received placebo in the 1st and 2nd injections and CYD dengue vaccine in the 3rd injection. The applicant's safety analyses included these two subjects in the control group. I consider it more appropriate to include these subjects in the CYD vaccine group after the subjects received the CYD dengue vaccine in the safety analyses. Since these subjects were not in the reactogenicity subset (hence no reactogenicity data were reported) and did not report any SAE within 6 months from the last vaccination or any related or fatal SAE beyond 6 months from the last vaccination, the only impact of misclassifying these subjects

- on the safety analyses is the total number of subjects in each treatment group. The impact on the calculation of AE occurrence is minimal.
2. Five subjects receiving the CYD dengue vaccine in the reactogenicity subset were not included in the solicited reaction analyses, such that the total number of subjects in these analyses was 692 instead of 697. Unlike Studies CYD14 or CYD15, where an indicator variable "REACTANA" was defined to flag subjects included in the reactogenicity analyses, this variable was not included for CYD23. In addition, the applicant only submitted analysis programs for unsolicited AEs and SAEs, but not for solicited reactions. I examined the FA domain and noticed that only 692 and 693 subjects responded to the questions of occurrence of administration site reaction and the questions of occurrence of systemic reaction, respectively. Therefore, noticing the minor discrepancy, I consider the missing solicited reaction data likely to have minimal impact on analysis results.
 3. A total of 9 unsolicited non-serious AEs had missing severity, 7 in the CYD vaccine group and 2 in the control group. Two of these AEs, one in each of the CYD vaccine group and control group were assessed as not related to the investigational product, while causality is missing for the other AEs. In the safety analyses, AEs with missing causality were considered related to the investigational product as a conservative approach.
 4. The analysis of non-serious adverse events included AEs within 28 days from the last vaccination, as specified by protocol. There were 2 non-serious AEs (nasopharyngitis and pharyngitis) reported beyond 28 days from the last dose, both in the CYD vaccine group and assessed as not related. The impact on the safety profile was minimal due to the small number of events, in my opinion.
 5. For the SAE analyses:
 - a. The analyses were based on two non-overlapping period, within 6 months from last injection and above 6 months from last injection. The applicant used Day 196, instead of Day 180 or 183, as the dividing point.
 - b. Subjects who did not receive all three injections and had SAEs were counted as subjects who have "SAE until 6 months after the last injection" regardless of the SAE onset time.
 - c. Table 4 summarizes only SAEs in the reactogenicity subset. For all subjects eligible for safety analyses, 309 out of 2668 (11.6%) of subjects in the CYD vaccine group and 172 out of 1329 (12.9%) subjects in the control group reported SAE within 180 days after the last injection, and 9 out of 2668 (0.3%) of subjects in the CYD vaccine group and 5 out of 1329 (0.4%) subjects in the control group reported SAE after 180 days from the last injection.

Overall, I did not identify any substantial imbalance between the CYD vaccine group and the control group.

The frequency of solicited systemic reactions was similar after a first injection of CYD dengue vaccine and rabies vaccine or placebo. After the subsequent CYD dengue vaccine or control injections, the frequency of solicited systemic reactions remained similar as compared to the previous injection. Overall, the safety profile tended to be similar after

any injection and after each injection in each vaccine group in terms of time to onset, number of days of occurrence, severity and resolution of solicited systemic reactions, which were mostly reported as Grade 1.

SAE

A total of 586 SAEs occurred during the study (584 occurred during the Active Phase). Among the 586 SAEs reported, only 1 was assessed as related to treatment by the Investigator. During the Active Phase, there were no differences in reported SAEs between treatment groups; 11.8% of subjects in the CYD vaccine group and 13.2% of subjects in the control group reported 366 and 218 SAEs, respectively. Among the 584 SAEs reported during the Active Phase, a total of 93 SAEs were reported by 87 subjects within 28 days after any injection (50 subjects with 56 SAEs in the CYD vaccine group [1.9%] and 37 subjects with 39 SAEs in the control group [2.8%]).

6.3.12.3 Deaths

Five unrelated deaths were reported, 4 occurred in the control group and 1 in the CYD vaccine group.

7. INTEGRATED OVERVIEW OF EFFICACY

Please refer to the statistical review of clinical efficacy data.

8. INTEGRATED OVERVIEW OF SAFETY

8.1 Safety Assessment Methods

AEs were assessed in terms of solicited injection site and systemic reactions, unsolicited non-serious events and SAEs. Seventeen main studies (see section 8.2.1) plus CYD10 and CYD11 collected data on immediate reactions. AEs leading to discontinuation were assessed only in main studies. SAEs were evaluated throughout the trials. The pooled safety analysis only considered the time periods “within 28 days” and “>28 days to 6 months” after each and any dose, by SOC, PT, seriousness criterion and outcome. SAEs after 6 months after each and any dose were not reported in all trials but only in CYD05, CYD22, CYD28, CYD23/CYD57, CYD14 and CYD15; the results are presented in the respective individual study CSRs. In order to permit the standardization of the coding system for AEs, solicited, unsolicited non-serious and serious AEs were re-coded according to MedDRA version 14.0

In addition, biological safety, CYD dengue vaccine viremia, and risk of clinically SVCD cases as assessed by IDMC were evaluated in the ISS.

The assessments were compiled by treatment group. Three sets of pools were utilized for analysis – main studies pool, secondary studies pool, and all studies combined pool.

8.2 Safety Database

8.2.1 Studies/Clinical Trials Used to Evaluate Safety

Twenty-two clinical studies that used the CYD dengue vaccine containing ~5 log₁₀ CCID₅₀ per serotype were included in the safety integrated and/or pooled analysis and were divided into 2 sets, which were main and secondary studies. The main studies consisted of the trials that implemented the final vaccine schedule (Day [D]0/Month [M]6/M12) and thus were used for the primary analyses. The secondary studies consisted of trials that evaluated other vaccine schedules.

The studies were categorized as follows:

- a. Seventeen main studies:
 - Children (≥ 2 years), adolescents, and adults: CYD12 (Group 1), CYD13, CYD14, CYD15, CYD17, CYD22, CYD23/CYD57, CYD24, CYD28, CYD30, CYD32, CYD47, and CYD51 (Group 1)
 - Infants and toddlers (i.e., from 9 months to < 2 years): CYD08, CYD29, and CYD33
- b. Six secondary studies:
 - Children (≥ 2 years), adolescents, and adults: CYD04, CYD05, CYD06, CYD10, CYD11, and CYD51 (Groups 2, 3 and 4)

CYD01, CYD02, and CYD12 (Groups 2 and 3) were not included as these studies did not utilize the CYD dengue vaccine dose of ~5 log₁₀ CCID₅₀. CYD63 and CYD64 data were not presented in this integrated analysis as the subjects received booster dose.

8.2.2 Overall Exposure, Demographics of Pooled Safety Populations

The pooled analysis for the SAEs and dengue cases evaluation was based on a dataset of 27643 subjects aged 9 months through 60 years who received at least 1 injection of the CYD dengue vaccine (final formulation and vaccination schedule), among which 20 426 subjects aged 9 through 45 years received at least 1 injection of the CYD dengue vaccine (1306 adults 18 to 45 years old, and 19 120 children and adolescents aged 9 to 17 years). The pooled analysis for reactogenicity evaluation was based on a dataset of 7576 subjects (subset of subjects from the previous dataset).

Of the subjects assessed for safety, 2091 aged 9 to 17 years, and 245 aged 18 to 45 years had available data on their dengue immune status at baseline.

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

All studies included in the pooled analyses were randomized, except for Study CYD10 in which 35 subjects 18 to 40 years of age were included. In particular, Studies CYD14, CYD15 and CYD23/57 contributed almost 95% of subjects 9 to 17 years of age in the safety database. Studies CYD23/57, CYD14 and CYD15 were randomized (2:1), placebo-controlled clinical trials with similar protocols, dose administered, duration of safety endpoint follow-up, and methods of safety data collection. Therefore, I have no major concerns regarding the pooling of the safety data. It should be noted, though, that the pooled

control group is a mixture of active controls and inactive control since placebo (inactive control) was used in some studies while active controls (e.g. rabies vaccine, flu vaccine, etc.) were used in other studies.

8.4 Safety Results

A safety overview in the subset of subjects aged 9 to 17 years for the Main Studies is presented in Table 5 for any injection of the CYD dengue vaccine or control.

Table 5. Safety Overview after any CYD dengue vaccine or placebo dose – Subjects 9-17 years – Main studies

Subjects experiencing at least one:	CYD dengue vaccine			Placebo		
	n/M	%	(95% CI)	n/M	%	(95% CI)
REACTOGENICITY SUBSET						
Immediate unsolicited AE	4/3067	0.1	(0.0; 0.3)	3/1478	0.2	(0.0; 0.6)
Immediate unsolicited AR	2/3067	<0.1	(0.0; 0.2)	1/1478	<0.1	(0.0; 0.4)
Grade 3 immediate unsolicited AR	1/3067	<0.1	(0.0; 0.2)	0/1478	0.0	(0.0; 0.2)
Solicited reaction	2271/3050	74.5	(72.9; 76.0)	1019/1471	69.3	(66.8; 71.6)
Grade 3 solicited reaction	356/3050	11.7	(10.6; 12.9)	126/1471	8.6	(7.2; 10.1)
Solicited injection site reaction	1556/3050	51.0	(49.2; 52.8)	602/1470	41.0	(38.4; 43.5)
Grade 3 solicited injection site reaction	45/3050	1.5	(1.1; 2.0)	13/1470	0.9	(0.5; 1.5)
Solicited systemic reaction	2043/3050	67.0	(65.3; 68.7)	934/1471	63.5	(61.0; 66.0)
Grade 3 solicited systemic reaction	338/3050	11.1	(10.0; 12.2)	123/1471	8.4	(7.0; 9.9)
Unsolicited non-serious AE	1362/3067	44.4	(42.6; 46.2)	625/1478	42.3	(39.8; 44.9)
Unsolicited non-serious AR	69/3067	2.2	(1.8; 2.8)	17/1478	1.2	(0.7; 1.8)
Grade 3 unsolicited non-serious AR	6/3067	0.2	(0.1; 0.4)	1/1478	<0.1	(0.0; 0.4)
Unsolicited non-serious injection site AR	41/3067	1.3	(1.0; 1.8)	8/1478	0.5	(0.2; 1.1)
Grade 3 unsolicited non-serious injection site AR	0/3067	0.0	(0.0; 0.1)	0/1478	0.0	(0.0; 0.2)
Unsolicited non-serious systemic AE	1351/3067	44.0	(42.3; 45.8)	623/1478	42.2	(39.6; 44.7)
Unsolicited non-serious systemic AR	30/3067	1.0	(0.7; 1.4)	9/1478	0.6	(0.3; 1.2)
Grade 3 unsolicited non-serious systemic AR	6/3067	0.2	(0.1; 0.4)	1/1478	<0.1	(0.0; 0.4)
Anaphylactic reaction (SMQ)	0/3067	0.0	(0.0; 0.1)	0/1478	0.0	(0.0; 0.2)
Non-serious allergic reaction (targeted list)	15/3067	0.5	(0.3; 0.8)	8/1478	0.5	(0.2; 1.1)
Non-serious Grade 3 allergic reaction (targeted list)	1/3067	<0.1	(0.0; 0.2)	0/1478	0.0	(0.0; 0.2)
Post vaccination dengue-like syndrome	2/3067	<0.1	(0.0; 0.2)	0/1478	0.0	(0.0; 0.2)
SAFETY ANALYSIS SET						
Discontinuation due to AE*	64/19120	0.3	(0.26; 0.43)	38/9490	0.4	(0.28; 0.55)
Serious allergic reaction (targeted list)	4/19120	<0.1	(0.01; 0.05)	1/9490	<0.1	(0.00; 0.06)
SAE ≤28 days post dose†	124/19120	0.6	(0.54; 0.77)	73/9490	0.8	(0.60; 0.97)
SAE >28 days to 6 months post dose†	538/19120	2.8	(2.58; 3.06)	310/9490	3.3	(2.92; 3.64)
Related SAE ≤28 days post dose	4/19120	<0.1	(0.01; 0.05)	2/9490	<0.1	(0.00; 0.08)
Related SAE >28 days to 6 months post dose	0/19120	0.0	(0.00; 0.02)	0/9490	0.0	(0.00; 0.04)
Neurological disorder SAE ≤30 days post dose	12/19120	<0.1	(0.03; 0.11)	9/9490	<0.1	(0.04; 0.18)
Neurological disorder SAE >30 days to 6 months post dose	25/19120	0.1	(0.08; 0.19)	13/9490	0.1	(0.07; 0.23)
Death within 6 months post dose	5/19120	<0.1	(0.01; 0.06)	4/9490	<0.1	(0.01; 0.11)
Related death within 6 months post dose	0/19120	0.0	(0.00; 0.02)	0/9490	0.0	(0.00; 0.04)

- n: number of subjects experiencing the endpoint

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

- CYD dengue vaccine ~5 log₁₀ CCID₅₀ per dose of serotypes 1, 2, 3 and 4. Main studies applied a D0/M6/M12 vaccine schedule

* Identified in the termination form as SAE or other AE.

† Two SAEs reported after the safety integrated analysis are not accounted for in this safety overview, one in each the “within 28 days” and one in the “>28 days to 6 months post dose” time windows.

- Contributing studies: CYD13 CYD14 CYD15 CYD22 CYD23 CYD24 CYD28 CYD30 CYD32

Source: Table 35 in the Clinical Summary of Safety.

The incidence of solicited injection site and systemic reactions tended to be slightly lower in the control group (41.0% and 63.5%, respectively) than in the CYD vaccine group (51.0% and 67.0%, respectively). A similar trend in incidence of Grade 3 solicited systemic reactions between the 2 groups (11.1% in the CYD vaccine Group vs. 8.4% in the Control Group) was observed. In the control group, the incidence of unsolicited non-serious AEs, unsolicited non-serious ARs, related SAEs within 28 days after any injection, serious and non-serious allergic reactions and neurological disorders within 30 days (42.3%, 1.2%, <0.1%, <0.1%, 0.5% and <0.1%, respectively) was similar to that of the CYD vaccine Group (44.4%, 2.2%, <0.1%, <0.1%, 0.5% and <0.1%, respectively).

Reviewer Comments

1. *There is a minor discrepancy between the age subgroup the safety analyses were performed (9-17 years) and the age group the CYD dengue vaccine is indicated for (9-16 years). I consider the safety subgroup analysis supportive for the indication of the vaccine because the majority of the subjects included in the 9-17 years subgroup were between 9 to 16 years of age. To be more specific, only 24 of the 19120 subjects included in the analyses were 17 years of age, 18 in the CYD vaccine group and 6 in the control group. A total of 8 AEs was reported by these 24 subjects, 6 in the CYD vaccine group and 2 in the control group, all of which are non-serious and not related to treatment. Of the 24 subjects, 15 in the CYD vaccine group and 3 in the control group reported solicited reaction, all of grade 1 or 2. Therefore, very similar safety analysis results are expected for 9 to 16 years, and the impact on the safety conclusions of including 17-year old subjects is minimal.*
2. *The 9490 subjects in the control group of the safety analysis set include those who received at least one dose of placebo and no CYD dengue vaccine. Subjects receiving other vaccines and no placebo were not included. I consider this acceptable because the number of such subjects is small (n=3), and excluding subjects who received active control appears to be more conservative since active control is likely more reactogenic than inactive control (placebo).*
3. *In the applicant's safety analyses, each safety event (solicited AE, unsolicited AE, etc.) is associated with the last investigational product the subject received. For example, if a subject received CYD dengue vaccine at Injection 1 and placebo at Injection 2, an AE occurred after Injection 2 was not counted as an AE in the CYD vaccine group by the applicant. I do not agree with this approach because chronologically the AE occurred after an injection of CYD dengue vaccine, although possibly far apart from the injection of CYD dengue vaccine, and one cannot rule out the possibility of the association between the AE and the CYD dengue vaccine. Nevertheless, I identified only one AE as such in subjects 9-16 years of age (gastrointestinal bacterial infection, which was considered serious and not related). Hence, I consider the impact minimal.*
4. *A total of 81 SAEs, all not related, were reported with partial starting dates where the onset day of SAE post last vaccination cannot be calculated exactly. These SAEs were excluded from the summary of SAEs ≤ 28 days post vaccination and SAEs > 28 days to 6 months post vaccination. I inspected the partial starting dates. Of these SAEs, 65 SAEs occurred at least one year after the last*

vaccination based on the partial dates. Hence, I agree with excluding these SAEs from the analysis. Of the other 16 SAEs, I was able to identify 9 SAEs (4 in the CYD vaccine group and 5 in the control group), 3 SAEs (2 in the CYD vaccine group and 1 in the control group), and 4 SAEs (2 in the CYD vaccine group and 2 in the control group) that were within 6 months from any vaccination, not within 6 months from any vaccination, and unable to determine whether they are within 6 months from any vaccination, respectively. Regardless of how to incorporate these SAEs in the safety analysis, the safety profile appears to be consistent.

5. *The analysis for SAEs >28 days to 6 months post vaccination was based on an indicator variable "SAE6MO" defined by the applicant to flag out SAEs occurring within 6 months of any vaccination. I compared this flag with the actual SAE onset day (if available) and noted that both variables are largely consistent, except that a few SAEs (5 in the CYD vaccine group and 2 in the control group) occurred more than 200 days after the last vaccination were flagged as SAEs within 6 months. I consider the impact minor.*

8.4.1 Deaths

In the CYD vaccine Group, 5 deaths (<0.1%) were reported within 6 months after any injection in the Main Studies, for the subjects aged 9 to 17 years. In the Control Group, 4 deaths (<0.1%) occurred in the Main Studies within 6 months after any Injection. None was assessed as related to the injection by the Investigator or the Applicant.

8.4.2 Nonfatal Serious Adverse Events

In the CYD vaccine Group, the proportion of subjects who experienced at least 1 SAE within 28 days after any injection was low (0.6%) and similar to that in the Control Group (0.8%). In both groups, most of the SAEs were in the SOC Infections and Infestations with 0.3% of subjects in both groups. SAEs in the other SOC were all reported in less than 0.1% of subjects.

In the CYD vaccine Group, the proportion of subjects who experienced at least 1 SAE after 28 days and up to 6 months after any injection was 2.8% and similar to that in the Control Group (3.3%). In the two groups, most of the SAEs were in the SOC Infections and infestations (1.5% of subjects in the CYD vaccine Group and 2.1% in the Control Group), Injury, Poisoning and procedural complications (0.5% of subjects in the CYD vaccine Group and 0.4% in the Control Group), and Gastrointestinal disorders (0.2% of subjects in both groups). SAEs in the other SOC were all reported in less than 0.1% of subjects. Appendicitis (0.4% in both groups), dengue fever (0.2% in the CYD vaccine Group and 0.6% in the Control Group) and gastroenteritis (0.1% in the CYD vaccine Group and 0.3% in the Control Group) were the PTs most frequently reported as SAEs.

8.4.3 Study Dropouts/Discontinuations

A total of 102 Subjects discontinued due to a non-serious AE or a SAE; i.e. 64 (0.3%) in the CYD vaccine Group and 38 (0.4%) in the Control Group for subjects 9-17 years in the main studies.

8.4.4 Common Adverse Events

Please refer to the medical officer's review.

8.4.5 Clinical Test Results

Please refer to the medical officer's review.

8.4.6 Systemic Adverse Events

In the CYD vaccine Group, the most frequent solicited systemic reaction within 14 days after any CYD dengue vaccine injection was headache (54.1%). Myalgia (42.0%) and malaise (40.9%) were also frequently reported. The incidence of asthenia was lower (34.2%), as that of fever (16.4%). Most solicited systemic reactions were Grade 1, occurred within 3 days after injection (except for fever, which appeared throughout the solicited period) and had between 1 and 3 days of occurrence. The incidence of all solicited systemic reactions except fever tended to decrease after each subsequent dose of vaccine. In the Control Group, the incidence of each solicited systemic reaction was similar to that of the CYD vaccine Group.

8.4.7 Local Reactogenicity

In the CYD vaccine Group, the most frequent solicited injection site reaction within 7 days after any CYD dengue vaccine injection was injection site pain (49.2%); erythema (8.4%) and swelling (6.9%) were less frequently reported. Most solicited injection site reactions were Grade 1, occurred within 3 days after injection and had between 1 and 3 days of occurrence. The incidence of pain, erythema, and swelling within 7 days tended to decrease after each subsequent dose of vaccine. In the Control Group, injection site pain was reported in a lower proportion of subjects (39.0%) than in the CYD vaccine Group, while erythema and swelling were reported at a similar frequency (7.5% and 5.1%, respectively).

8.4.8 Adverse Events of Special Interest

Please refer to the medical officer's review.

8.5 Additional Safety Evaluations

Reactogenicity by dengue baseline status in subjects 9 to 17 years old

Among the 2842 subjects aged 9 to 17 years old who participated in study arms evaluating the final CYD dengue vaccine formulation with the final schedule and assessed for dengue status at baseline, 2091 dengue immune and 751 dengue non-immune at baseline received at least 1 dose of the CYD dengue vaccine. Of them, 2008 immune and 718 non-immune subjects received 3 doses of CYD dengue vaccine. In the Control Group, 1021 immune and 348 non-immune subjects received at least 1 injection of placebo and 792 and 223, respectively, received 3 placebo injections.

After any injection, the incidence of solicited injection site reactions tended to be higher in the CYD vaccine Group than in the Control Group, in both immune (48.1% versus 40.8%, respectively) and non-immune (54.7% and 38.2%) subjects. The frequencies of

the other parameters as well as the frequency of Grade 3 reactions were similar between the two groups for both immune and nonimmune subjects.

The reactogenicity profile of vaccinated baseline dengue immune and non-immune subjects, was similar. Solicited injection site reactions tended to be slightly more frequently reported in dengue non-immune vaccinated subjects (54.7%) than in dengue immune vaccinated subjects (48.1%). Solicited systemic reactions were reported in 66.0% of dengue immune subjects and in 67.8% of dengue non-immune subjects. Unsolicited non-serious ARs were reported in 1.9% of dengue immune subjects and in 3.6% of dengue non-immune subjects. The percentage of Grade 3 reactions was also similarly reported among immune and non-immune subjects. SAEs within 28 days post any injection occurred with similar frequencies in immune and non-immune subjects (0.6% vs. 0.7%, respectively).

Reviewer Comments

The safety analyses by dengue baseline serostatus were performed on subjects whose baseline dengue PRNT results are available (immunogenicity subset). The safety profiles for dengue immune subjects and dengue non-immune subjects appear similar. I did not identify increased risks for dengue immune subjects.

Hospitalized VCD and clinically-severe VCD (SVCD)

The incidence of hospitalized VCD and SVCD was evaluated by a pooled analysis of CYD23/57, CYD14, and CYD15. While no evidence of increased risk of hospitalized VCD or SVCD was observed in the CYD vaccine Group compared to the Control Group during the 25-month observation period of the active phase in each of the 3 efficacy studies or in the pooled analysis, there was a trend of increased risk of hospitalized VCD and SVCD for young CYD dengue vaccinees.

For subjects 2 to 8 years old, over the 3 years of Hospital Surveillance/Phase-SEP, a total of 131 subjects out of 4801 in the CYD vaccine Group and 57 out of 2394 in the Control Group reported hospitalized VCD cases due to any serotype. The annual incidence rate over the 3 years was 0.9% in the CYD vaccine Group and 0.8% in the Control Group. The occurrence of hospitalized VCD tended to be slightly higher in the CYD vaccine Group compared to the Control Group (RR: 1.146 [95% CI: 0.83; 1.59]) over the three-year study period. An increased risk was observed in Year 1 (RR: 1.576 [95% CI: 0.81; 3.31]), which decreased in Year 2 (RR: 0.908 [95% CI: 0.56; 1.49]) and tended to increase in Year 3 (RR: 1.234 [95% CI: 0.69; 2.31]). This trend was especially marked in children aged 2 to 5 years in whom the RR was 1.241 (95% CI: 0.58; 2.90) in Year 2 Hospital Phase compared to 4.953 (95% CI: 1.20; 43.71) in Year 1 Hospital Phase, and increased back to 2.393 (95% CI: 0.89; 8.03) in Year 3 Hospital Phase/SEP.

This imbalance, however, was not observed in older age groups. For subjects 9 to 16 years old, over the 3 years of Hospital Surveillance/Phase-SEP, a total of 76 subjects out of 16,788 in the CYD vaccine Group and 71 out of 8389 in the Control Group reported hospitalized VCD cases due to any serotype. The annual incidence rate over the 3 years was 0.2% in the CYD vaccine Group and 0.3% in the Control Group. The occurrence of

hospitalized VCD was lower in the CYD vaccine Group compared to the Control Group and this decreased risk was similar in each of the three years. The RR over the entire three-year period was 0.535 (95% CI: 0.38; 0.75).

The observation of the imbalance in the occurrence of hospitalized dengue cases in the youngest age group during the first year of the Hospital Phase has been interpreted by some within the scientific community as a possible indication of an increased risk of dengue hospitalization or severe dengue illness in individuals who have not been exposed to dengue prior to being vaccinated with CYD dengue vaccine. This hypothesis cannot be adequately evaluated with existing data from the CYD dengue studies, because pre-vaccination samples were only obtained for a small proportion of participants (immunogenicity subsets) and because the incidence of dengue hospitalization or severe dengue is much lower than the incidence of any symptomatic VCD, resulting in partial and largely imprecise estimates of the risk according to prior exposure to natural dengue infection.

Nevertheless, since blood samples were collected for all study participants approximately 1 month after the third injection of CYD dengue vaccine or placebo (Month 13), efforts have been made to characterize baseline dengue serostatus (through statistical modelling) of study participants at this time-point. However, the Dengue PRNT50 is directly affected by the immune responses induced by the vaccine. As such, a positive PRNT50 value at M13 can be the result of either prior dengue exposure or CYD dengue vaccination. The applicant developed an ELISA against non-structural protein 1 (NS1) to detect previous natural infection of dengue disease as opposed to previous exposure to CYD dengue vaccine, because it is expected that previous exposure to CYD dengue vaccine is not likely to induce meaningful levels of antibody against the dengue NS1 protein.

Utilizing the NS1 results, the applicant conducted a series of post-hoc exploratory analyses to investigate the impact of baseline dengue serostatus on risks of hospitalized VCD and SVCD, based on a case-cohort study. The exploratory analyses include:

- a. Using the M13 NS1 to impute baseline dengue status (excluding subjects with documented dengue infection before M13) with a threshold of 9 EU/mL or 20 EU/mL.
- b. Applying the method of multiple imputation to impute baseline dengue serostatus based on M13 NS1 results as well as other demographic variables.
- c. Applying the method of super-learner to impute baseline dengue serostatus based on M13 NS1 results as well as other demographic variables.

The risk of dengue hospitalization and SVCD, over the entire duration of the study occurring after M0 in subjects classified as seronegative and seropositive by the multiple imputation (MI) method is summarized in Table 6.

Table 6. Relative Risk against hospitalized VCD and SVCD due to any serotype during the entire study up to M60-M72 – by age (2-8 and 9-16 years old) and dengue serostatus by PRNT measured or imputed – MI

	Age group	Baseline status	Study	CYD dengue vaccine Cases/M	Placebo Cases/M	Hazard Ratio (95% CI)
Hospitalized Dengue	2-8 years	Seropositive	CYD14+CYD57	93.6 (313.2)	89.8 (156.4)	0.504 (0.331, 0.767)
		Seronegative	CYD14+CYD57	137.4 (192.8)	37.2 (100.6)	1.949 (1.192, 3.186)
	9-16 years	Seropositive	CYD14+CYD15+CYD23/57	58.8 (1502.9)	137.7 (729.8)	0.206 (0.138, 0.307)
		Seronegative	CYD14+CYD15+CYD23/57	64.2 (375.1)	25.3 (207.2)	1.412 (0.743, 2.682)
SVCD	2-8 years	Seropositive	CYD14+CYD57	23.9 (313.2)	20 (156.4)	0.578 (0.257, 1.304)
		Seronegative	CYD14+CYD57	30.1 (192.8)	5 (100.6)	3.311 (0.874, 12.536)
	9-16 years	Seropositive	CYD14+CYD15+CYD23/57	11.2 (1502.9)	33.4 (729.8)	0.158 (0.068, 0.371)
		Seronegative	CYD14+CYD15+CYD23/57	14.8 (375.1)	3.6 (207.2)	2.435 (0.472, 12.559)

- M: total number of subjects selected in sub-cohort
- Cases and M are average numbers from 10 iterations of multiple imputations
- Study group classified as treated (Subjects classified as CYD Dengue Vaccine Group if received at least 1 injection of CYD dengue vaccine)

Source: Modified from Tables 10 and 12 in 2.5 Clinical Overview.

During the entire follow-up period, a decreased risk of hospitalized VCD was observed in both 9 to 16 years old and 2 to 8 years old subjects classified as baseline seropositive using NS1 supplemental analysis. The decreased risk was observed against all four serotypes in the two age groups, but this risk reduction was of higher magnitude in subjects 9 to 16 years compared to 2 to 8 years (HR: 0.206 [95% CI: 0.138;0.307] and HR: 0.504 [95% CI:0.331; 0.767], respectively). An increased risk of hospitalized VCD in all subjects classified as seronegative was observed over the entire study duration.

Similarly, a decreased risk of clinically SVCD was observed during the entire study in both 9 to 16 years old and 2 to 8 years old vaccinated subjects classified as seropositive at baseline but this risk reduction was of higher magnitude in subjects 9 to 16 years compared to subjects 2 to 8 years (HR: 0.158 [95% CI: 0.068, 0.371] and HR: 0.578 [95% CI: 0.257, 1.304], respectively). An increased risk of clinically SVCD was observed in vaccinated subjects 2 to 16 years of age classified as seronegative. HR was 2.435 (95% CI: 0.472, 12.559) in the age group of 9 to 16 years and HR was 3.311 (95% CI: 0.874, 12.536) in the age group of 2 to 8 years.

Analyses based on other methods lead to similar conclusion as the multiple imputation method. The applicant concluded that

- In seronegatives, there is a statistically significant increased risk of hospitalized and severe dengue over the long-term follow-up.
- In seropositives, there is a long-term benefit of the vaccine with statistically significant decreased risk against hospitalized and severe dengue over the long-term follow-up.

Reviewer Comments

The NS1 analysis results are largely consistent with the analysis results based solely on the immunogenicity subset (Tables 123 and 130 in Summary of Clinical Safety), with the

exception that the NSI analyses have larger effective sample size due to the predicted baseline serostatus via complex statistical models. The analyses are considered exploratory and post-hoc in nature because of the large body of model assumptions and limitations, which include but are not limited to:

- a. The proportion of subjects whose baseline dengue serostatus are missing and need imputation is too large. The statistical model to predict baseline dengue status was developed based on at most ~12% of the subjects in CYD14, CYD15, and CYD23/57 only. Hence, the statistical model may not be adequate to predict baseline dengue status for the entire group of subjects included in the case-cohort study.*
- b. The applicant analyzed the data as a case-cohort study, where a randomly selected sub-cohort of the total cohort is required. However, the expanded sub-cohort in the analyses was not randomly selected from the total cohort, although reasonable efforts have been made by the applicant to repair this sub-cohort for Studies CYD14 and CYD15 by randomly selecting proportions of subjects from the immunogenicity subset and subjects recruited after the immunogenicity subset was full, based on the percentages of subjects recruited before and after the immunogenicity subset was full. In addition, the 300 subjects with known baseline dengue status in Study CYD23 were not randomly selected and there was no remedy available.*

Nevertheless, the analyses appear reasonable under the data limitations. For example, the applicant's approach of sub-cohort selection deviated from the assumption of randomness, but increased the number of subjects with known baseline dengue status to be included in the analysis to offset some uncertainty associated with predicting baseline dengue status. In addition, the applicant applied three different statistical models (using the Month 13 NSI results, multiple imputation, and super-learner) stemming from different angles: using the Month 13 NSI results eliminates the need for a complicated statistical imputation model; the method of multiple imputation was based on a parametric model (logistic regression); the super-learner model was based on a non-parametric model. Hence, overall, I consider the NSI exploratory model reasonably robust and informative.

8.5.1 Dose Dependency for Adverse Events

Please refer to the medical officer's review.

8.5.2 Time Dependency for Adverse Events

Please refer to the medical officer's review.

8.5.3 Product-Demographic Interactions

Please refer to the medical officer's review.

8.5.4 Product-Disease Interactions

Please refer to the medical officer's review.

8.5.5 Product-Product Interactions

Please refer to the medical officer's review.

8.5.6 Human Carcinogenicity

Please refer to the medical officer's review.

8.5.8 Immunogenicity (Safety)

Not applicable.

8.6 Safety Conclusions

The reactogenicity profile of the CYD dengue vaccine in terms of incidence, severity, and nature of events was generally similar to that reported after injection of placebo, although in adults, the incidence of several clinical safety parameters had higher incidence in the CYD vaccine Group than in the Control Group. SAEs within 28 days after any injection were reported in approximately 1% of subjects in the CYD vaccine group or the placebo group. Deaths were reported with a similar frequency in both Dengue and Control Groups. No deaths were assessed as related to the study vaccine in any study. The reactogenicity profile of vaccinated baseline dengue immune and non-immune subjects, was similar. No increased risk was observed for the indicated population.

The NS1 supplemental study investigated vaccine safety by dengue serostatus over the long-term follow-up period (follow-up of 60 to 72 months post dose 1) in the 3 efficacy studies, and complemented analyses performed in the immunogenicity subsets which had limited precision. The NS1 supplemental study found that dengue serostatus at baseline likely modified the risk of hospitalized dengue and severe dengue after vaccination. In subjects classified as dengue seropositive (subjects previously exposed to natural dengue infection), a decreased risk against hospitalized and severe dengue over the long-term follow-up period was observed following vaccination in subjects 2-16 years of age and particularly in subjects ≥ 9 years. In subjects classified as dengue seronegative prior to dengue vaccination, an increased risk of dengue hospitalization and severe dengue following vaccination was observed in subjects 2-16 years of age.

10. CONCLUSIONS

In conclusion, there were no major safety issues related to this submission, except that the safety profile against hospitalized VCD and SVCD cases appears to be more favorable in older children. The additional exploratory analysis results with NS1 assay indicate that baseline serostatus is reasonably likely a risk modifier for hospitalized VCD and SVCD. However, given that the NS1 analyses are post-hoc and rely on various assumptions of the complicated statistical model, I consider the NS1 analyses exploratory and supportive in nature due, and defer to the medical reviewer regarding the overall acceptability of the NS1 analysis results, as well as the overall safety of the vaccine in individuals 9 to 16 years with laboratory-confirmed previous dengue infection.