Australian Government
Department of Health
Therapeutic Goods Administration

AusPAR Attachment 2

Extract from the Clinical Evaluation Report for live, attenuated, chimeric dengue virus (serotypes 1, 2, 3 and 4)

Proprietary Product Name: Dengvaxia

Sponsor: Sanofi-Aventis Australia Pty Ltd

First round report: September 2016
Second round report: March 2017
Safety Related Request with data: June 2018

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

Contents

List of abbreviations

Abbreviation	Meaning
Ab	Antibody
ACV	Advisory Committee on Vaccines
AE	Adverse event
AESI	Adverse event of special interest
ALT	Alanine aminotransferase
AND	Acute neurotropic disease
AP	Asia Pacific
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification
AVD	Acute viscerotropic disease
CCID50	Cell-culture infectious dose 50%
CDP	Clinical Development Program
CI	Confidence interval
DF	Dengue fever
DHF	Dengue haemorrhagic fever
DP	Drug product
DS	Drug substance
DSS	Dengue shock syndrome
E	Envelope
EDC	Estimated Date of Conception
ELISA	Enzyme-linked immunosorbent assay
EMA	European Medicines Agency
FASE	Full analysis set for efficacy
FASI	Full analysis set for immunogenicity

Abbreviation	Meaning
FDA	US Food and Drug Administration
FV	Flavivirus
GMT	Geometric mean titre
GMTR	Geometric mean of titre ratio
HSA	Human serum albumin
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
Latin America	Latin America
LMP	last menstrual period
MedDRA	Medical Dictionary for Regulatory Activities
mFASE	Modified full analysis set for efficacy
MMR	Measles/mumps/rubella
MN	Microneutralisation
NS1	Non-structural 1
PoC	Proof of concept
PPSE	Per-protocol analysis set for efficacy
prM	Pre-membrane
PRNT	plaque reduction neutralisation test
PT	Preferred term
RMP	Risk Management Plan
RT-PCR	Reverse transcription-polymerase chain reaction
SAE	Serious adverse event
SC	Subcutaneous
SEA	South East Africa
SOC	System Organ Class

Abbreviation	Meaning
SVCD	Severe virologically confirmed dengue
VCD	Virologically confirmed dengue
VE	Vaccine efficacy
WBC	White blood cells
WHO	World Health Organisation
YF	Yellow fever

1. Introduction

This is a submission to register a new clinical entity.

This is a vaccine. The proposed indication for the CYD dengue vaccine is for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in individuals 9 through 60 years of age living in endemic areas.

2. Clinical rationale

Following administration, the live attenuated dengue viruses replicate locally and elicit neutralising antibodies and cell-mediated immune responses against the four dengue virus serotypes.

3. Contents of the clinical dossier

3.1. Scope of the clinical dossier

A total of 28,894 subjects aged 9 months to 60 years were randomised in the studies presented in the application, to receive at least one injection of a tetravalent CYD dengue vaccine, regardless of the formulation. Among these subjects:

- 28,653 received at least one injection of the CYD dengue vaccine (final formulation regardless of the schedule) and were included in the safety database, in which the occurrence of serious adverse events (SAEs) and adverse events of special interest (AESIs) was assessed. A total of 27,643 subjects received the final formulation with the final schedule.
- 7,576 subjects provided data to assess the reactogenicity of the final formulation of the CYD dengue vaccine.

The main objectives of the CDP were to characterise the candidate vaccine in terms of efficacy, safety and immunogenicity profiles, when assessed in different regions, in different age groups and in populations with various degrees of endemicity, from highly endemic to non-endemic. There is currently no licensed dengue vaccine and no immunological correlate of protection has currently been established. Therefore, the efficacy of the CYD dengue vaccine has been assessed in endemic areas in one proof of concept (PoC) Phase IIb mono-centre study (Study CYD23 conducted in Thailand) and 2 pivotal Phase III studies performed in 10 countries of southeast Asia Pacific (AP) and Latin America (Latin America) (Study CYD14 in AP and Study CYD15 in Latin America).

The majority of studies, including the studies assessing the final formulation of the vaccine given with the final schedule, were randomised, controlled and at least blind observer studies. All serology testing was performed in a blinded manner. During the long-term safety follow-up of the efficacy studies, investigators and subjects remain blinded to the vaccine received during the Active Phase of the study, that is, from inclusion to 25 months after the first injection.

As of December 2015, the CDP includes 25 clinical studies, completed (21) or on-going (4):

- 5 Phase I studies
- 14 Phase II studies
- 6 Phase III studies.

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, 21,215 subjects were aged 9 through 60 years and received at least one injection of the final formulation of the CYD dengue vaccine, regardless of the schedule. Results from 24 clinical studies are described in the present application (Study CYD56 is ongoing).

3.1.1. Phase I and early Phase II studies

The first clinical study conducted as part of the CDP of the vaccine, Study CYD01, assessed safety and immunogenicity of a monovalent vaccine against dengue virus serotype 2. All remaining Phase I studies (Studies CYD02, CYD04, CYD05, and CYD06) evaluated the safety of the CYD dengue vaccine first in adults from non-endemic areas (Studies CYD02 and CYD04) and in a second step in adults and children in non-endemic (Study CYD06) and in an endemic area (Study CYD05). The studies were first conducted in non-endemic areas to collect data from subjects who are non-immune to flaviviruses, and especially to dengue. Because of the risk of severe disease, it was important that subjects included in the first studies not be at risk of natural infection with dengue or other flaviviruses. These Phase I studies together with 3 Phase II studies (Studies CYD10, CYD11 and CYD12) provided data on safety and immune response induced by several formulations of the vaccine and different schedules of vaccination. The results of these 8 studies supported the selection of the final vaccine formulation and schedule, that is, approximately 5 $\log^{10}$ $CCID_{50}$ of each live, attenuated, dengue serotype 1, 2, 3, 4 virus given as 3 injections 6 months apart.

3.1.2. Late Phase II studies

Based on safety and immunogenicity results from the above-mentioned studies, 5 additional Phase II studies (Studies CYD13, CYD22, CYD24, CYD28 and CYD30) were initiated in different endemic countries in Asia Pacific and Latin America to further evaluate the safety and immunogenicity of the CYD dengue vaccine in different populations (that is, age, baseline flavivirus (FV) status, region) following 3 injections of the final formulation administered 6 months apart. A PoC efficacy study (Phase IIb) was then initiated in Thailand (Study CYD23) in children aged 4 to 11 years, for whom a safety follow-up is ongoing (Study CYD47) to assess safety and immunogenicity of the CYD dengue vaccine in Indian subjects, as required by local authorities for registration.

A PoC co-administration Phase II study (Study CYD08) was also conducted to evaluate the co administration of CYD dengue vaccine together with measles/mumps/rubella (MMR) vaccine in toddlers below 2 years of age.

Additionally, clinical investigations into a shorter schedule adapted to traveller/non-endemic populations were initiated via 2 Phase II studies in adults in the US (Studies CYD51 and CYD56). Study CYD51 is completed and CYD56 is ongoing.

3.1.3. Phase III studies

Two Phase III efficacy studies, each statistically powered to independently demonstrate efficacy, were designed and prepared to be carried out in parallel in 10 endemic countries: Study CYD14 (5 countries in AP, 2 to 14 year old children) and CYD15 (5 countries in Latin America, 9 to 16 year old children and adolescents). Enrolment started prior to availability of the supportive PoC Phase IIb results.

Four other Phase III clinical studies (Studies CYD17, CYD29, CYD32 and CYD33) were also conducted:

- The CYD17 study had a primary objective to demonstrate the consistency of 3 commercial scale lots (Phase III lots) in a non-endemic population. Study CYD17 also provided safety and immunogenicity information on the new bulk process of Phase III lots in comparison to Phase II lots and data bridging the Phase II lots to the Phase III lots.

- The CYD32 study was a Phase III study to evaluate safety and immunogenicity of the vaccine in a paediatric population in Malaysia.
- The 2 other Phase III studies investigated concomitant administration with vaccines given to infants and toddlers below 2 years of age: YF co-administration with the first injection of CYD dengue vaccine from 12 months of age in Peru and Colombia (Study CYD29) and co-administration of DTacP-IPV booster with the second injection of the CYD dengue vaccine from 15 months of age in Mexico (Study CYD33).

3.1.4. Duration of follow-up

In all studies but in Studies CYD04 and CYD06, safety was followed up to at least 6 months after the last injection.

The majority of the clinical database consists of subjects aged 9 months to 45 years at high risk of dengue disease. Less data are currently available in adults more than 45 years old: a total of 241 adults from 46 to 60 years of age received the CYD dengue vaccine in Study CYD17, conducted in a non-endemic area. No data are available from adult subjects aged 46 to 60 years living in an endemic area. In addition, a limited number of adults (668 subjects from 18 to 45 years old) in endemic population received the CYD dengue vaccine. The clinical studies did not include adults aged more than 60 years old or children below 9 months. The safety database in subjects aged 9 through 60 years allows for the detection of very common, common and uncommon adverse events (AEs) as recommended by the WHO. Thus, a possibility of rare (that is, with the frequency less than 0.1%) AEs going undetected cannot be excluded.

The clinical module includes reports for:

- 8 Clinical pharmacology studies providing for PD/dosage and safety data.
- 10 Phase II efficacy and safety studies.
- Interim report on long term follow up Study CYD57.
- One proof of concept study (Study CYD23).
- 2 pivotal efficacy/safety studies.
- 1 lot to lot consistency study
- Case report forms with safety data.
- Safety integrated analysis report, immunogenicity and efficacy integrated analysis report.
- Immune and viro assay details
- Literature references.

3.2. Paediatric data

Most of the studies submitted in this application include paediatric data.

3.3. Good clinical practice

All clinical studies evaluating the CYD dengue vaccine comply with the Quality Standards of the International Conference on Harmonisation (ICH) guidelines, the Food and Drug Administration (FDA) guidelines for Good Clinical Practice (GCP), EU Directive 2001/20/EC and the EMA guidelines on clinical evaluation of new vaccines clinical study reports in the submission state the studies complied with CPMP/ICH/135/95 Note for Guidance on Good Clinical Practice.

4. Pharmacokinetics

Not applicable.

5. Pharmacodynamics

In accordance with the EMA Guideline on Clinical Evaluation of New Vaccines, the pharmacodynamic profile for the CYD dengue vaccine was defined by its immunogenicity profile.

6. Dosage selection for the pivotal studies

6.1. Pharmacokinetics and pharmacodynamics: dose finding studies

The choice of parental strains, that is, the strains from which the vaccine was derived, within the assay was made in order to ensure optimal assessment of vaccine induced immune response by using the matched vaccine antigens.

The objectives of the first clinical studies were to define the formulation, the dosage and the schedule of administration of the CYD dengue vaccine. Eight clinical studies (5, Phase I studies and 3 Phase II studies) were conducted for that purpose. These studies were mainly conducted in adult subjects (except 2 Phase I studies conducted in children, adolescents and adults) living in non-endemic areas. Only 1 study, Study CYD05, was conducted in endemic areas (the Philippines).

6.1.1. Choice of formulation (tetravalent vaccine) and concentration

6.1.1.1. Tetravalent vaccine

Study CYD01 assessed safety and immunogenicity of a single dose of monovalent chimeric dengue 2 vaccine (Chimerivax-DEN2) containing 5 or 3 $\log_{10}$ plaque forming units (PFU)) and showed that one dose of monovalent chimeric dengue 2 vaccine induced a satisfactory immune response against serotype 2 and low seropositivity rates to the other 3 serotypes (in YF non-immune subjects), confirming the need for a tetravalent vaccine.

A tetravalent vaccine against the 4 serotypes was tested in Study CYD04 and showed satisfactory safety and immunogenicity profiles in FV non-immune adults, and, in Study CYD05 and Study CYD06, in different age groups (2 to 45 years) and FV backgrounds. The immunogenicity response varied across populations due to co-factors (that is, age, baseline status and region). Seropositivity rates against all 4 serotypes after 3 injections of a tetravalent formulation ranged from 39.1% (Study CYD04, FV non-immune adults) to 85.0% (Study CYD05, FV immune adults, adolescents, and children).

The choice of a tetravalent formulation was confirmed by the use of sequential or simultaneous bivalent formulations in Study CYD11, which did not improve the immune response compared to the tetravalent formulation.

6.1.1.2. 5555 Formulation

The Phase I study CYD01 showed that single administration of ChimeriVax-DEN2 at either 5 $\log_{10}$ PFU or 3 $\log_{10}$ PFU was safe and immunogenic in both YF non-immune and YF immune subjects. Based on these findings, the mid-range concentration of 4 $\log_{10}$ $CCID_{50}$ of tetravalent ChimeriVax DEN was chosen for Study CYD02. The concentration of 5 $\log_{10}$ $CCID_{50}$ of tetravalent ChimeriVax DEN was chosen for Studies CYD04, CYD05, and CYD06 and provided an immune response against all four serotypes. In Study CYD12, the safety and immunogenicity of 3 CYD

dengue vaccine formulations were assessed: 5555 (5 log_{10} for each of the 4 serotypes), 5553 (5 log_{10} for serotypes 1, 2, and 3 and 3 $log_{10}$for serotype 4), and 4444 (4 log_{10} for each of the 4 serotypes). The 5553 formulation was intended to improve the immune response by taking into account the immuno-dominance of serotype 4 observed in previous studies.

In CYD12, the 5555 formulation showed a trend toward higher seropositivity rates to the 4 serotypes after the third injection (62.9%) than the 5553 formulation (59.3%) and the 4444 formulation (53.3%). The 4444 formulation induced similar GMTs to those with the 5555 formulation, however, seropositivity rates to all 4 serotypes tended to be lower. Considering the GMTs, the 5553 formulation elicited the highest GMTs to serotypes 1, 2, and 3 (57.1 (1/dil) to 114 (1/dil)), while the GMT for serotype 4 (25.9 (1/dil)) was lower than that with the other formulations. The 4444 formulation elicited similar GMTs to the 5555 formulation but with a trend toward lower GMTs for serotype 3. The different vaccine formulations assessed in CYD12 showed that different concentrations of a given serotype can impact the immune response to the other serotypes. Safety profile of the different formulations was acceptable and similar. The formulation at approximately 5 log_{10} $CCID_{50}$ per serotype (5555) reliably provided an immune response against all 4 serotypes after 3 injections in various populations, regardless of age, region, FV status at baseline, and was selected for further Phase II and Phase III studies.

6.1.2. Choice of vaccination schedule

The vaccination schedule was selected mainly based on the results from Phase I studies, that is, Studies CYD02, CYD04, CYD05 and CYD06. The choice of schedule was then supported by data from Phase II studies, particularly Study CYD12. The main parameters for the selection of the number of injections and the dosing interval were the achievement of an acceptable immune response against the 4 dengue serotypes in a timely manner, in all subjects included in the CDP, that is, regardless of age, region and of baseline immune status to dengue.

In Studies CYD04, CYD05 and CYD06 studies, groups having received the tetravalent vaccine administered at a 3-injection regimen at 0, 3/4, 12 months provided information on different categories (adults, adolescents, and children), different regions (non-endemic USA and Latin America, and endemic Asia Pacific) and different baseline FV status at baseline (FV non-immune versus immune subjects). The data showed that increasing the interval between injections had a beneficial effect on the overall immunogenicity outcome.

Overall across the studies, there was a trend toward progressive increase in GMTs and seropositivity rates after each dengue injection, with a decrease between injections. After 3 injections of the 5 log_{10} concentration, the seropositivity rates against all 4 serotypes ranged from 39.1% (Study CYD04, FV non-immune adults) to 85.0% (Study CYD05, FV immune adults, adolescents, and children). A predominant response to serotype 4 was observed after the first injection of the CYD dengue vaccine in these 3 studies. The second and the third injections induced an increase in GMTs for all serotypes in baseline FV non-immune subjects.

Within Studies CYD05 and CYD06 including children, adolescents, and adults in both non-endemic and endemic regions, younger children appear to benefit the most from the third injection to achieve a broad immune response against the 4 serotypes. In addition, the benefit of the third injection in terms of immune response was more marked in baseline FV non-immune populations, who tended to have a lower immune response after 2 injections in Studies CYD04, CYD06, and within Study CYD05 conducted in an endemic region.

Three injections provided the best approach to achieve a consistent immune response against all 4 serotypes in all evaluated populations.

The interval between the first and second injections was evaluated in Phase I Studies CYD04 and CYD05 which investigated 3 injections of the approximately 5 log_{10} concentration at 0, 3/4 and 12 months in the dengue group and 2 injections at 0 and 8/9 months in the Control group.

An intra-study group comparison between Study CYD05 subjects who received 2 injections of the CYD dengue vaccine either 3/4 months apart or 8/9 months apart showed a trend toward higher GMTs when the second injection was given 8 to 9 months after the first injection in children and adolescents in endemic regions (Study CYD05). These observations suggested that increasing the interval between injections contributes to a higher immune response. Study CYD12 was the first Phase II study testing the final 5 log_{10} concentration with a 6 month interval between injections. Study CYD12 immunogenicity results confirmed that 3 injections at a 6 month interval provided a satisfactory immune response to the 4 serotypes, with 62.9% of FV non-immune adult subject being seropositive against all 4 serotypes. Additionally, Phase I and II study observations suggested that increasing the interval between injections resulted in an increase in Ab response.

6.1.3. Cellular immune response

The CMI response was assessed in a subset of adult and adolescents subjects in Studies CYD04, CYD10, CYD11, and CYD28. First, there was no evidence of increase in inflammatory responses after immunisation with the CYD dengue vaccine; no increase of innate pro-inflammatory cytokine production or other markers of sensitisation to severe outcomes of dengue were observed. Second, regarding adaptive T cell responses, in volunteers seronegative at baseline, the CYD dengue vaccine induced serotype-specific Th1/Tc1 responses to structural antigens from all four dengue serotypes, as well as CD8/Tc1 responses to YF17D non-structural (NS)3 antigen. After three injections of CYD dengue vaccine, a balanced cellular response was induced against all four serotypes, and these serotype-specific T cell responses paralleled the neutralising Ab responses measured by PRNT50 assay. CD8/Tc1 responses directed against dengue NS3 were also boosted by the CYD dengue vaccine in individuals dengue-immune at baseline. Regarding the cytokine profile, the vaccine induced a cellular response with a Th1/Tc1 profile wherein interferon-γ (IFN- γ) dominates over tumour necrosis factor α (TNF-α) and Th2 cytokines including interleukin-13 (IL-13). This suggests that over-inflammatory and potentially detrimental dengue-specific responses would not be recalled upon a subsequent dengue infection in vaccinees, while dengue- specific T cell help to B cells would be beneficial to increase and accelerate neutralising Ab responses.

6.2. Evaluator's conclusions on dose finding for the pivotal studies

There were a number of phase I and II studies performed to examine the dose and scheduling of the CYD vaccine. These were performed in adults, and then children, both in non-endemic and endemic areas. They were conducted initially in non-endemic regions to ensure that there were no negative consequences from subsequent natural infection. The benefit of 3 injections on the seropositivity rate was observed, especially in younger age groups and/or baseline FV non-immune populations. There were no substantial differences in terms of GMTs levels post-injection-3 compared to post-injection 2, but as GMTs decreased between injections, subjects benefit from the third injection to increase the levels of GMTs.

The schedule with 3 injections at 6 month intervals was further confirmed with subsequent studies conducted in different settings (age, baseline FV status) using the same Phase II lots of the final formulation with the chosen schedule.

7. Clinical efficacy

7.1. Studies providing evaluable efficacy data

The evaluation of efficacy of the CYD dengue vaccine is based on the vaccine efficacy (VE) observed in the 2 pivotal Phase III efficacy Studies CYD14 and CYD15. Supportive clinical data

were obtained from Study CYD23, a Phase IIb PoC efficacy study. Additionally, immunogenicity data were obtained from 16 studies in subjects aged 9 months to 60 years that assessed the final formulation of the CYD dengue vaccine given in a 3 dose-schedule at 6 month intervals: Studies CYD12a, CYD17 and CYD51 in non-endemic regions and Studies CYD08, CYD13, CYD14, CYD15, CYD22, CYD23, CYD24, CYD28, CYD29, CYD30, CYD32, CYD33 and CYD47 in endemic regions. Specific analyses of immune responses as they related to efficacy were performed in data generated in Studies CYD14 and CYD15 efficacy studies.

The main objective of the immunogenicity studies was to describe the humoral immune response induced by 3 injections of CYD dengue vaccine administered 6 months apart in both endemic and non-endemic populations with age, previous exposure to dengue and other FV and region as key variables.

The main objective of the efficacy studies was to demonstrate VE of the CYD dengue vaccine in preventing virologically confirmed dengue (VCD) cases, in accordance with WHO guidelines on dengue vaccine evaluation. The large scale efficacy studies also allowed for the assessment of the relationship between the occurrence of VCD cases and the level of neutralising Ab titre 28 days after the third injection.

7.1.1. Criteria for assessment

7.1.1.1. Humoral immune response

The PRNT assay was used to assess the immunogenicity of the CYD dengue vaccine through the measurement of neutralising Ab at varying time points. The PRNT was performed by the applicant's laboratory, for all studies that assessed the final formulation.

7.1.1.2. Immunological and virological assay methods

For the majority of subjects, the humoral immune response was assessed before and approximately 30 days after each injection.

The following parameters were used to characterise the humoral immune response induced by the CYD dengue vaccine:

- GMTs expressed in reciprocal of dilution (1/dil) for each serotype.
- GMTRs from baseline to post-vaccination for each serotype.
- Seropositivity rate, defined as the proportion of subjects with a neutralising Ab titre ≥ 10 (1/dil). This level also corresponds to the lower limit of quantification (LLOQ) of the PRNT assay. Seropositivity rate was assessed for each serotype and cumulatively for at least one, two, three and four serotypes. Initial assessment of immune response to dengue vaccine was based upon experiences with JE vaccination and the associated correlate of protection primarily in non-endemic populations. As experience accumulated in endemic populations of different ages and regions, GMT became the most important criteria for the dose assessment.

7.1.1.3. Cellular immune response

In order to further characterise the immune response induced by the CYD dengue vaccine and as recommended in the WHO, EMA guidelines, cell-mediated immunity was also assessed in some studies in adolescents and adults in endemic and non-endemic regions (Studies CYD04, CYD10, CYD11 and CYD28).

7.2. Pivotal or main efficacy studies

The two large scale Phase III efficacy studies were randomised, placebo controlled, observer-blinded and stratified by age. Studies CYD14 and CYD15 are described together because of the identical structure. These trials were similar in all respects apart from geographical location.

Each individual study was sufficiently powered to demonstrate significant efficacy of the CYD dengue vaccine in preventing the occurrence of VCD due to any serotype after 3 injections, given 6 month apart with a time window of ± 20 days for the second and third injections. The choice of the countries and sites for the Phase III efficacy studies was based on national surveillance data and available data from epidemiological studies showing that these countries were highly endemic and have had evidence of all 4 serotypes circulating. The choice was confirmed by the results of the 2 prospective cohort studies conducted by the applicant prior to the initiation of the studies. These data provided an estimate of the dengue attack rate in the study target population (3.4% of VCD cases in Asia Pacific and 1.2% of VCD in Latin America).

7.2.1. Study CYD14 and Study CYD15

7.2.1.1. Study design, objectives, locations and dates

For both Study CYD14 and 15, study design, dengue cases were accrued through an active surveillance phase starting on the day of the first injection and until 13 months following the third injection. As recommended by the WHO Guideline, efficacy was assessed through the detection of symptomatic VCD cases, regardless of severity, occurring more than 28 days after completion of the vaccination schedule (primary objective).

The primary objective of the efficacy studies was to assess the efficacy of the CYD dengue vaccine after 3 injections 6 months apart in preventing the occurrence of symptomatic VCD cases, regardless of severity, due to any of the 4 serotypes. The assessment period extended from 28 days after the third injection to the end of the Active Phase, that is, 13 months post-injection 3. The primary endpoint in efficacy studies was defined as: 'Symptomatic VCD cases' occurring more than 28 days after the third injection up to the end of the Active Phase.

The studies were divided into Active and Hospital phases:

- Active Phase: During the Active Phase, surveillance was designed to maximise the detection of symptomatic confirmed dengue. For each subject, the Active Phase of dengue case detection began after the first injection (Dose 1) and was expected to continue until 13 months after the third injection (Dose 3). The continuation of the Active Phase for 13 months post-Injection 3 is based on this 12 month period beginning 28 days after Dose 3.
- Hospital Phase: This phase began after the Active Phase. Subjects with a febrile illness and requiring hospitalisation were screened for dengue. This phase is currently ongoing and will continue until trial completion. In this phase, there is a minimum frequency of one contact every 3 months and surveillance of identified non-study healthcare sites is being performed.

Study CYD14 is a randomised, observer blind, placebo controlled, multi-centre, Phase III trial in 10,278 subjects. Subjects received 3 vaccinations (Day 0, Day 0 + 6 months, Day 0 + 12 months), with an efficacy follow-up of 13 months after Dose 3 and a follow-up for hospitalised dengue cases of 60 months after Dose 3. It was conducted across 11 sites in Indonesia, Malaysia, Thailand, the Philippines, and Vietnam (2 to 3 sites in each country). Subjects were randomised in a 2 to 1 ratio to 2 groups:

- CYD Dengue Vaccine Group (N = 6852): CYD dengue vaccine at 0, 6 and12 months
- Control Group (N = 3426): placebo at 0, 6 and12 months.

A subset of subjects from each country was evaluated for reactogenicity and immunogenicity to enable the generation of country-specific data on reactogenicity, immunogenicity, and baseline dengue and Japanese encephalitis (JE) antibody (Ab) levels. Between 300 and 600 subjects were targeted to be enrolled in each participating country, to a total of 2000 subjects (1333 in the CYD Dengue Vaccine Group and 667 in the Control Group). Study CYD14 was conducted June 2011-December 2014.

CYD15 is a multi-centre, randomised, observer blind, placebo controlled, multi-centre, Phase III trial in 5 countries, conducted at 22 sites across Brazil, Colombia, Honduras, Mexico, and Puerto

Rico (approximately 1 to 9 sites in each country) involving 20,875 subjects. This study was conducted between June 2011 and April 2014. Children and adolescents aged 9 to 16 years were randomised in a 2 to 1 ratio to receive 3 injections (at 0, 6, and 12 months) of either product:

- CYD Dengue Vaccine: N = 13,917 (CYD Dengue Vaccine Group)
- Placebo (NaCl 0.9%): N = 6958 (Control Group).

Immunogenicity and reactogenicity were assessed in a subset of 2000 subjects (1333 in the CYD Dengue Vaccine Group and 667 in the Control Group). This subset of subjects was evaluated to enable the generation of country-specific data on reactogenicity, immunogenicity, and baseline dengue and yellow fever (YF) antibody (Ab) levels.

7.2.1.2. Inclusion and exclusion criteria

An individual had to fulfil all of the following criteria in order to be eligible for trial enrolment:

- Aged 2 to 14 years on the day of inclusion and resident of the site zone.
- Subject in good health, based on medical history and physical examination.
- Consent form has been signed and dated by the subject (based on local regulations), and informed consent form has been signed and dated by the parent(s) or another legally acceptable representative (and by an independent witness if required by local regulations).
- Subject able to attend all scheduled visits and to comply with all trial procedures.

An individual fulfilling *any* of the following criteria was to be excluded from trial enrolment:

- Subject is pregnant, or lactating, or of childbearing potential (to be considered of non-childbearing potential, a female must be pre-menarche, surgically sterile, or using an effective method of contraception or abstinence from at least 4 weeks prior to the first vaccination until at least 4 weeks after the last vaccination).
- Participation in another clinical trial investigating a vaccine, drug, medical device, or a medical procedure in the 4 weeks preceding the first trial vaccination.
- Planned participation in another clinical trial during the present trial period.
- Self-reported or suspected congenital or acquired immunodeficiency; or receipt of immunosuppressive therapy within the preceding 6 months; or long-term systemic corticosteroids therapy (prednisone or equivalent for more than 2 consecutive weeks within the past 3 months).
- Self-reported seropositivity for Human Immunodeficiency Virus (HIV) infection.
- Self-reported systemic hypersensitivity to any of the vaccine components, or history of a life-threatening reaction to the vaccine used in the trial or to a vaccine containing any of the same substances.
- Chronic illness that, in the opinion of the Investigator, is at a stage where it might interfere with trial conduct or completion.
- Receipt of blood or blood derived products in the past 3 months, which might interfere with assessment of the immune response.
- Planned receipt of any vaccine in the 4 weeks following any trial vaccination.
- Deprived of freedom by administrative or court order, or in an emergency setting, or hospitalised involuntarily.
- Current alcohol abuse or drug addiction that might interfere with the ability to comply with trial procedures.

- Identified as a site employee of the Investigator or study centre, with direct involvement in the proposed study or other studies under the direction of that Investigator or study centre, as well as a family member of the site employees or the Investigator.

Temporary Contraindications

A prospective subject should not have been included in the study until the following condition and/or symptoms were resolved:

- Febrile illness (temperature ≥ 38.0°C) or moderate or severe acute illness/infection (according to Investigator judgment) on the day of vaccination.
- Receipt of any vaccine in the 4 weeks preceding the first trial vaccination.

7.2.1.3. Study treatments

CYD dengue vaccine

Each 0.5 mL dose of reconstituted vaccine contained 4.5 – 6 $\log_{10}$ cell-culture infectious dose 50% ($CCID_{50}$) of each live, attenuated, dengue serotype 1, 2, 3, 4 virus.

Placebo

Solution NaCl 0.9% SC

7.2.1.4. Efficacy variables and outcomes

The primary outcome was 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 aged 2 to 14 years at the time of inclusion.

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

- Acute febrile illness (that is, temperature ≥ 38°C on at least 2 consecutive days).
- Virologically confirmed by dengue RT-PCR and/or dengue NS1 ELISA Ag test. It was expected 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 each subject until 13 months after Dose 3.

Secondary efficacy objectives:

- Dengue cases were taken into account if they occurred more than 28 days after the respective vaccination.
- Safety - Occurrence of SAEs, including serious AESIs, in all subjects.

Other Objectives:

- Detection of Dengue Cases during the Active Phase and grading of these.
- Neutralising Ab level against each of the four parental dengue virus strains of CYD dengue vaccine constructs were measured after the third injection at least in the immunogenicity and reactogenicity subset and in the subjects with a confirmed dengue infection.

7.2.1.5. Randomisation and blinding methods

Each subject who met the inclusion criteria and none of the exclusion criteria and signed an ICF/AF was randomly assigned to one of two groups via an IVRS, according to a 2 to 1 ratio (2 subjects included in the CYD Dengue Vaccine Group for 1 subject included in the Control Group). Subjects randomised in the study during the first 2 months of enrolment were also randomised in the subset of subjects evaluated for the immunogenicity and reactogenicity in each country.

An observer blind procedure was followed for the three injections of CYD dengue vaccine or placebo.

7.2.1.6. Analysis populations

Efficacy analyses were done on the per-protocol analysis set for efficacy (PPSE) (primary objective) and/or in the full analysis set for efficacy (FASE). The PPSE included all subjects who received 3 injections and who were compliant with the protocol. The FASE included all subjects who received at least one injection. Analyses done in the PPSE were done on VCD cases that occurred from 28 days post-injection 3 to the end of the Active Phase. Analyses done in the FASE were done on VCD cases that occurred throughout the Active Phase, that is, during the first 25 months of the study. Vaccine efficacy was also assessed in the modified FASE (mFASE) which included all subjects who received 3 injections, regardless of the per-protocol criteria. Analyses done in the mFASE were done on VCD cases occurring from 28 days post-injection 3 to the end of the Active Phase. Analyses of VE by dengue immune status at baseline were done in Full Analysis Sets for Immunogenicity (FASI) including subjects from the immunogenicity subsets in Studies CYD14 and CYD15.

7.2.1.7. Sample size

The planned sample sizes of Studies CYD14 (N = 10,278) and CYD 15 (N = 20,875) were calculated based on an estimated yearly incidence of VCD cases of 1.3%, a randomisation ratio of 2:1, an expected efficacy of the vaccine of 70% after 3 injections, a drop-out rate of 20% and assuming a 90% power to show a significant VE, that is, with a lower bound of the 95% CI of VE higher than 25%. The estimation of the yearly incidence was based on available epidemiological and cohort studies conducted in countries, where each study takes place. In Study CYD15, the planned sample size (N = 20,875) was calculated based on the same assumptions except an estimated yearly-incidence of dengue of 0.64%. This incidence rate was based on the median incidence rates of reported dengue cases in the pre- selected municipalities.

7.2.1.8. Statistical methods

The statistical methodology for the primary outcome was based on the use of the two-sided 95% confidence interval (CI) of the vaccine efficacy (VE) after the complete schedule of injections had been received by the subjects.

The first analysis was performed to assess the VE after the complete schedule of injections had been received by the subjects. This analysis was done on the per-protocol analysis set for efficacy (PPSE) after the completion of the Active Phase, and then was confirmed on the modified full analysis set for efficacy (mFASE).

Analysis for the primary objective

The following hypotheses (H) were tested using an alpha = 2.5%

- H_0: VE ≤ 25%
- H_1: VE > 25%

The statistical methodology was based on the use of the two-sided 95% CI of the VE. Then a second analysis of VE was also performed on the mFASE population. All subjects with a virologically confirmed dengue case occurring more than 28 days after the third dose were considered as cases for this mFASE during the Active Phase. Additional stratified analyses were conducted to take into account the different countries and/or other covariates.

Assessment of efficacy by pre-defined age ranges, and with age as a continuous variable was conducted as well as specific assessment of the claimed population where data was available (9 to 16 years).

7.2.1.9. Participant flow

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.

7.2.1.10. Major protocol violations/deviations

In relation to dengue detection in Studies 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.

7.2.1.11. Baseline data Study CYD14

Trial Population

A total of 10,275 subjects were randomised: 6851 in the CYD Dengue Vaccine Group and 3424 in the Control Group. A total of 2000 subjects, 1336 in the CYD Dengue Vaccine Group and 664 in the Control Group, were included in the immunogenicity and reactogenicity subset.

Overall, 10,194 subjects (99.2%) completed the Active Phase of the study and 10,143 (98.7%) completed the first year of the Hospital Phase. The same percentage was observed in the subset (99.2% and 98.8%, respectively for the Active Phase and for the Hospital Phase). A total of 10,272 subjects (3 were not vaccinated) were included in the FASE and 10,060 subjects were included in the PPSE.

Demographic characteristics

In the PPSE, there were similar percentages of female (51.5%) and male subjects (48.5%). 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. The mean age at enrolment was 8.8 years. The demographic characteristics were well-balanced between the treatment groups and comparable across the different populations (randomised subjects, FASE, SafAS, and FASI) and across countries.

In the immunogenicity and reactogenicity subset, the proportion of dengue immune subjects at baseline (neutralising Ab response ≥ 10 (1/dil) using Dengue PRNT50) increased with age: from 51.3% for the 2 to 5 years age group to 81.0% for the 12 to 14 years age group. Differences in terms of dengue status at baseline were observed across countries: from 47.8% of dengue immune subjects at baseline in Malaysia to 80.8% in Indonesia.

7.2.1.12. Baseline data study CYD15

Demographic and baseline characteristics

Overall, there were 9476 female (50.3%) and 9358 male subjects (49.7%) included in the PPSE; the mean age at enrolment was 12.4 years. The ethnic origin of the subjects was American Indian (16.2%), Caucasian (8.0%), Black (3.1%) but most of subjects reported being Hispanic of mixed ethnic origins, classified as 'Other' (72.6%). Demographic characteristics were very similar in the 2 treatment groups.

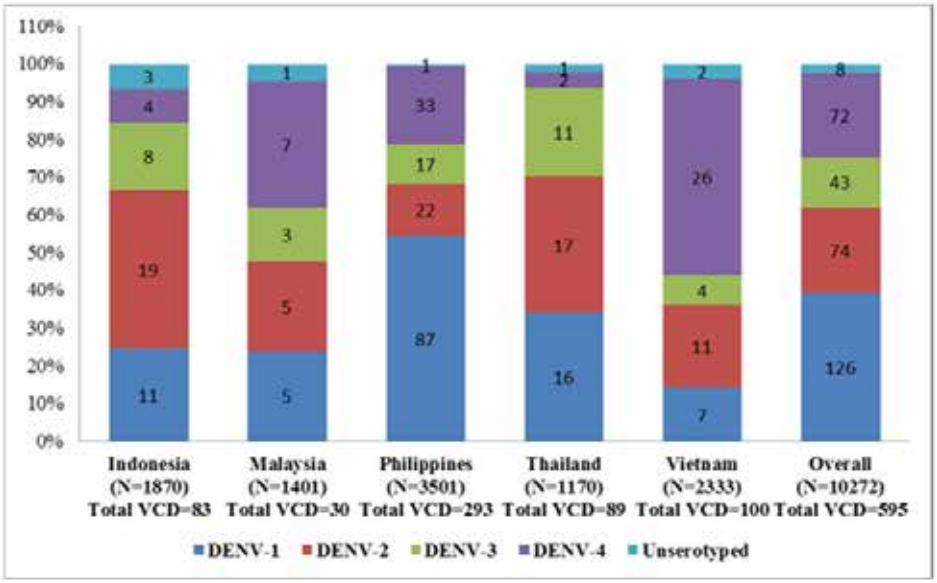
Overall, 79.4% of the subjects were dengue-seropositive at baseline. Percentages were similar in both treatment groups. Baseline dengue-seropositivity rates varied by country and were higher in Colombia (92.2%) and Honduras (85.7%) compared to the other countries such as Mexico (53.1%) and Puerto Rico (56.2%).

Dengue and YF seropositivity rates were similar in both age groups, although slightly higher in the older age group (74.9% and 77.1% for dengue and YF respectively in the 9-11 years age group vs. 83.8% and 82.3% for dengue and YF respectively in the 12-16 years age group). The demographic characteristics were comparable across the different populations of analyses.

7.2.1.13. Results for the primary efficacy outcome for both studies

During the Active Phase of Study CYD14, all 4 serotypes were circulating in the 5 countries and within each individual country with a different serotypes distribution as shown in Figure 1. The density incidence of virologically confirmed dengue (VCD) in children in the Control Group was 4.7% during the 25-month active surveillance period (that is, the Active Phase) and 4.1 % during the post-dose 3 period (that is, from 28 days post-dose 3 until the end of the Active Phase). During the Active Phase, the density incidence varied across serotypes with 1.9%, 1.1%, 0.6%, and 1.0% in the Control Group for serotypes 1, 2, 3, and 4, respectively. This serotype distribution was similar between the Active Phase and the post-dose 3 period. In Study CYD14, in the PPSE, a total of 250 subjects reported at least 1 VCD case from 28 days post-injection 3 to the end of the Active Phase. The overall primary estimate of VE against VCD post-injection 3 due to any serotype was 56.5% (Table 1) and the primary objective was met with a lower bound of 95% CI above 25%. This result was confirmed in the FASE population, including all VCD cases that occurred during the first 25 months of the study in all subjects having received at least one injection, with a VE of 54.8%. In subjects aged 9 to 14 years, VE was confirmed and was even higher than in the overall population and was of 67.8% after at least one injection.

Figure 1: Study CYD14 Distribution of virologically confirmed dengue per serotype and country in the Control Group during the Active Phase - Full Analysis Set for Efficacy



Total VCD = all VCD cases in the dengue and control groups

Table 1: Study CYD14 results efficacy primary endpoints

Primary Objective

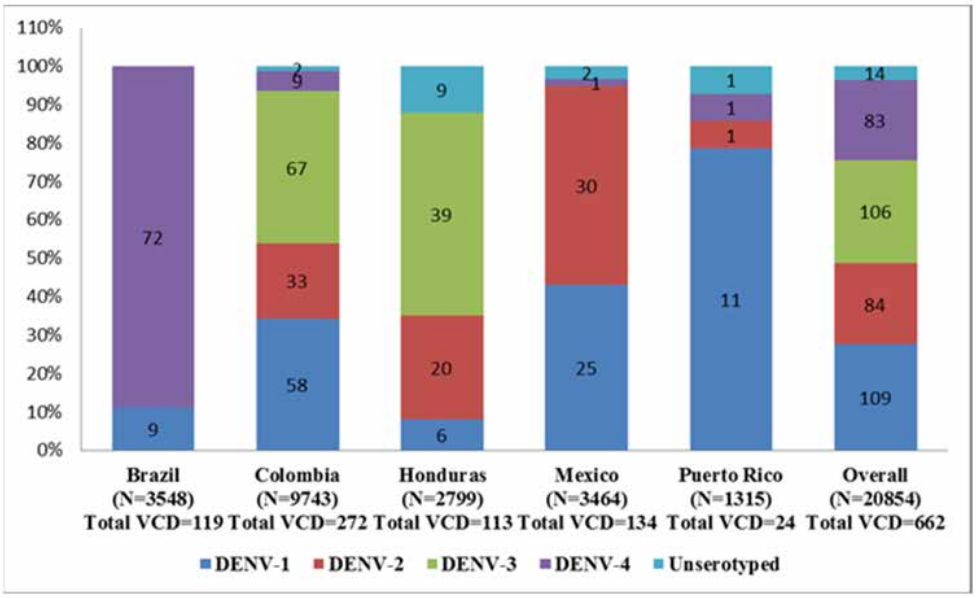
Vaccine Efficacy (VE) Against VCD Due to Any Serotype – Post-dose 3 (PPSE)

	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)

In Study CYD15 the incidence of dengue in the Control Group was 2.9% during the Active Phase. All 4 serotypes were detected during the Active Phase of the study, as shown in Figure 2. In Study CYD15, in the PPSE, a total of 397 subjects reported at least 1 VCD case from 28 days post-injection 3 to the end of the Active Phase. The overall primary estimate of VE against VCD from

28 days post-injection 3 to the end of the Active Phase due to any serotype was 60.8% (Table 2), and the primary objective was met with a lower bound of 95% CI above 25%. This result was confirmed in the FASE population, which included all VCD cases that occurred during the first 25 months of the study in all subjects having received at least one injection with a VE of 64.7%.

Figure 2: Study CYD15 Distribution of virologically confirmed dengue per serotype and country in the Control Group during the Active Phase - Full Analysis Set for Efficacy



Total VCD = all VCD cases in the dengue and control groups

Table 2: Study CYD15 Primary efficacy

Vaccine efficacy against symptomatic VCD post-Injection 3 due to any of the 4 serotypes - PPSE

	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)

Combined results of Studies CYD14 and CYD15

Overall, 55% to 65% VE was observed in preventing occurrence of VCD cases due to any serotype after at least one injection of the CYD dengue vaccine (Table 3). Significant VE was also observed in preventing the occurrence VCD cases due to each serotype after at least one injection of the CYD dengue vaccine. This varied according to the serotype: moderate efficacy was observed for serotypes 1 and 2 and high efficacy was observed for serotypes 3 and 4. This finding was consistent across the endemic regions evaluated. VE estimates in subjects aged 9 to 16 years are summarised for all endpoints in each individual study and in the meta-analysis in Table 4.

Table 3: Studies CYD14/CYD15 Vaccine efficacy against VCD cases due to any serotype

		Dengue Group		Control Group		Vaccine Efficacy	
Study	Analysis population	N	Cases	N	Cases	%	(95% CI)
CYD14	All subjects PPSE	6709	117	3350	133	**56.5**	(43.8; 66.4)
	All subjects FASE	6848	286	3424	309	**54.8**	(46.8; 61.7)
	9-14 years FASE	3316	90	1656	136	**67.8**	(57.7; 75.6)
CYD15	All subjects PPSE	12573	176	6261	221	**60.8**	(52.0; 68.0)
	All subjects FASE	13914	277	6940	385	**64.7**	(58.7; 69.8)
CYD14+ CYD15	All subjects PPSE	NC	NC	NC	NC	**59.2**	(52.3; 65.0)
	All subjects FASE	NC	NC	NC	NC	**60.3**	(55.7; 64.5)
	9-16 years FASE	NC	NC	NC	NC	**65.6**	(60.7; 69.9)

Table 4: VE estimates in Subjects aged 9 to 16 years during the active phase (FASE)

	CYD14 VE % (95%CI)	CYD15 VE % (95%CI)	CYD14+CYD15 VE % (95%CI)
Any serotype	67.8 (57.7; 75.6)	64.7 (58.7; 69.8)	65.6 (60.7; 69.9)
Serotype 1	65.7 (46.6; 78.2)	54.8 (40.2; 65.9)	58.4 (47.7; 66.9)
Serotype 2	36.8 (-10.1; 63.3)	50.2 (31.8; 63.6)	47.1 (31.3; 59.2)
Serotype 3	69.5 (31.9; 87.0)	74.2 (58.8; 81.7)	73.6 (64.4; 80.4)
Serotype 4	87.9 (75.5; 94.6)	80.9 (70.9; 87.7)	83.2 (76.2; 88.2)
Severe VCD cases (IDMC)	90.9 (58.4; 99.0)	95.5 (68.8; 99.9)	93.2 (77.3; 98.0)
DHF meeting any WHO criteria	90.9 (58.4; 99.0)	95.0 (64.9; 99.9)	92.9 (76.1; 97.9)
Hospitalized VCD	81.6 (60.7; 92.0)	80.3 (64.7; 89.5)	80.8 (70.1; 87.7)
Any serotype in dengue immune subjects	79.2 (47.2; 92.7)	83.7 (62.2; 93.7)	81.9 (67.2; 90.0)
Any serotype in dengue non-immune subjects	61.6 (-21.1; 88.1)	43.2 (-61.6; 80.0)	52.5 (5.9; 76.1)

7.2.1.14. Results for other efficacy outcomes

VE by serotype

VE was analysed by serotype from 28 days post-injection 3 to the end of the Active Phase, that is, to 1 year post-injection 3, (mFASE) and in the FASE, that is, throughout the Active Phase. From 28-days post-injection 3 to the end of the Active Phase (mFASE), VE is demonstrated for all 4 serotypes in Study CYD15 and for serotypes 1, 3 and 4 in Study CYD14 (Table 5). In both studies, VE varies across serotypes and is similar to VE estimates observed throughout the Active Phase. Data in the FASE, that is, throughout the Active Phase, are presented in Figure 3 in all subjects. VE is demonstrated for all 4 serotypes in Studies CYD14 and CYD15 after at least one injection. In both studies, VE varies across serotypes:

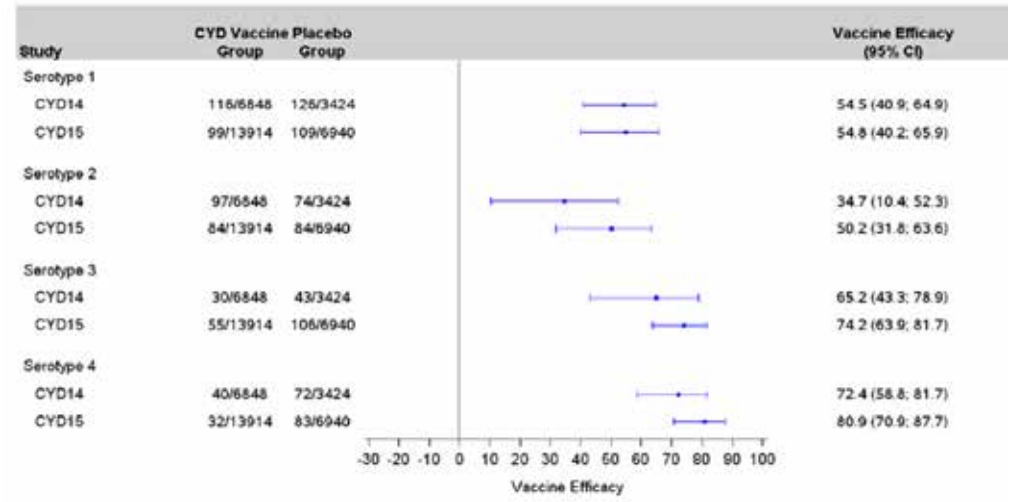
- Moderate VE is observed for serotype 1 (around 54% in both studies) and for serotype 2 (34.7% and 50.2% in Studies CYD14 and CYD15, respectively).
- High VE is observed for serotypes 3 (65.2% and 74.2% in Studies CYD14 and CYD15, respectively) and serotype 4 (72.4% and 80.9% in Studies CYD14 and CYD15, respectively). In both studies and for each serotype, the lower bound of the 95% CI lies above 0. In the meta-analysis pooling results from Studies CYD14 and CYD15, similar trends were observed. VE estimate against each serotype was 54.7% for serotype 1; 43.0% for serotype 2; 71.6% for serotype 3 and 76.9% for serotype 4.

Table 5: CYD14 results efficacy secondary endpoints

	Post-Dose 2			Post-Dose 3			Active Phase		
	Number of cases CYD vs Control	VE (%)	(95% CI)	Number of cases CYD vs Control	VE (%)	(95% CI)	Number of cases CYD vs Control	VE (%)	(95% CI)
Any serotype	205/238	57.9	(49.0; 65.2)	118/134	56.5	(43.8; 66.3)	286/309	54.8	(46.8; 61.7)
Serotype 1	80/91	56.7	(40.9; 68.3)	51/50	50.0	(24.6; 66.8)	116/126	54.5	(40.9; 64.9)
Serotype 2	70/56	37.9	(10.1; 56.9)	38/29	35.0	(-9.2; 61.0)	97/74	34.7	(10.4; 52.3)
Serotype 3	20/34	70.7	(47.7; 84.0)	10/23	78.4	(52.9; 90.8)	30/43	65.2	(43.3; 78.9)
Serotype 4	32/60	73.6	(58.7; 83.3)	17/34	75.3	(54.5; 87.0)	40/72	72.4	(58.8; 81.7)

Post-dose 2: period from 28 days post-dose 2 to the end of the Active Phase (OEAS) 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)

Figure 3: Forrest plot for VE against symptomatic VCD cases during the whole Active Phase due each of the 4 serotypes (FASE)



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.

Severe VCD

In both studies, vaccination was shown to provide clinically important reduction in severe disease including DHF due to dengue:

- Overall, in Study CYD14, IDMC assessment of severe dengue determined that the vaccine reduced the occurrence of severe VCD by 70% (based on 12 clinically SVCD cases in the Dengue Group and 20 clinically SVCD cases in the Control Group). The vaccine reduced the occurrence of DHF of any grade according to the WHO criteria by 80.0% (based on 8 DHF of any grade in the Dengue Group and 20 in the Control Group). In subjects aged 9 years and over, higher VE estimates were observed (90.9% for both IDMC and DHF VCD cases).
- In Study CYD15, the occurrences of clinically SVCD cases as assessed by IDMC and of DHF of any grade according to the WHO classification were reduced by at least 95% (based on 1 clinically SVCD cases in the Dengue Group and 11 in the Control Group, and based on 1 DHF of any grade in the Dengue Group and 10 in the Control Group).
- In the meta-analysis pooling Studies CYD14 and CYD15 data, VE in all subjects in preventing clinically SVCD (IDMC assessment) and DHF of any grade as per WHO criteria was of 79.1%

and 85.0%, respectively, throughout the Active Phase, confirming that both Phase III efficacy studies have a positive impact on occurrence of clinically severe and WHO severe VCD cases. In subjects aged 9 years and above, the occurrences of clinically SVCD as assessed by IDMC and of VCD cases meeting DHF criteria of any grade according to the WHO classification were reduced by at least 92%.

- In both studies, VE against clinically SVCD cases (as per IDMC definition) was also assessed by serotype. Limited data were obtained as only few cases were reported, but the analysis showed that all four serotypes contribute to the overall VE against SVCD cases, no serotype predominated.

Hospitalised dengue cases

Study CYD14 active phase

A total of 101 subjects, 40 in the CYD Dengue Vaccine Group and 61 in the Control Group, were hospitalised with VCD during the Active Phase. Overall, a reduction of more than 67% of the incidence of hospitalised dengue cases due to any serotype in subjects receiving at least 1 dose was observed in CYD Dengue Vaccine Group as compared to Control Group (relative risk (RR): 0.328 (95% CI: 0.21; 0.50)).

Post-dose 3, 55 subjects, 20 in the CYD Dengue Vaccine Group and 35 in the Control Group, were hospitalised with VCD. Overall, a reduction of more than 71% of the incidence of hospitalised dengue cases due to any serotype was observed in the CYD Dengue Vaccine Group as compared to the Control Group (RR: 0. 286 (95% CI: 0.16; 0.51)).

Study CYD14 hospital phase

During the first year of the Hospital Phase, a total of 40 hospitalised VCD episodes due to any serotype were observed in 40 subjects: 27 in the CYD Dengue Vaccine Group out of 6778 subjects and 13 in the Control Group out of 3387 subjects, representing a RR against hospitalised VCD cases of the vaccinees compared to the Control Group of 1.038 (95% CI: 0.52; 2.19). The RR against hospitalised VCD cases during the entire study was 0.459 (95% CI: 0.32; 0.65) in favor of a decreased risk of hospitalised VCD cases in the CYD Dengue Vaccine Group.

Study CYD15 active phase

During the Active Phase, a total of 60 subjects were hospitalised for a VCD case that is, 17 in the CYD Dengue Vaccine Group and 43 in the Control Group. All serotypes. Overall, an 80.3% reduction of the incidence of hospitalised dengue cases due to any serotype in subjects receiving at least 1 dose was observed in CYD Vaccine Group, compared to the Control Group, as indicated by the relative risk (RR): 0.197 (95% CI: 0.11; 0.35).

From 28 days post-Injection 3 to the end of the Active Phase, a total of 40 subjects were hospitalised for a VCD case. Overall, a reduction of the incidence of hospitalised VCD cases due to any serotype was observed in CYD Vaccine Group compared to the Control Group, as indicated by a RR of 0. 214 (95% CI: 0.10; 0.43).

Study CYD15 hospital phase

During the first year of the Hospital Phase, 31 hospitalised VCD episodes due to any serotype were observed in 31 subjects: 16 in the CYD Dengue Vaccine Group out of 13,268 subjects and 15 in the Control Group out of 6630 subjects. The corresponding annual incidence rate of hospitalised VCD cases was 0.1% in the CYD Dengue Vaccine Group and 0.2% in the Control Group, representing a RR of the vaccinees compared to the Control Group of 0.533 (95% CI: 0.25; 1.16). A slight increase of the RR against hospitalised VCD cases during the first year of the Hospital Phase was observed when compared to the Active Phase. The RR against hospitalised VCD cases during the entire study (from D0 to the end of the first year of the Hospital Phase) was < 1: RR of 0.284 (95% CI: 0.18; 0.44), in favour of a decreased risk of hospitalised VCD cases in the CYD Dengue Vaccine Group compared to the Control Group.

During the first year of the Hospital Phase, serotypes were identified in all dengue cases. The main serotypes were serotypes 1 and 2 in the 2 study groups (13 cases out of 16 in the CYD Dengue Vaccine Group and all cases in the Control Group). No cases from serotype 4 were observed in any groups.

7.2.1.15. Immunogenicity data

Seropositivity against at least 1, 2, 3 or 4 serotypes (FASI)

Baseline seropositivity rates (percentages of subjects with neutralising Ab titres ≥ 10 (1/dil)) against at least 1 serotype were similar in both treatment groups.

At baseline, in the FASI, the percentage of subjects seropositive against at least 1, 2, 3 or 4 serotypes, were similar across the 2 treatment groups. Seropositivity at baseline against all 4 serotypes was 42.0% in the CYD Dengue Vaccine Group and 40.8% in the Control Group. In the CYD Dengue Vaccine Group, the percentages of subjects seropositive increased post-injection 2 and post-injection 3 (84.9% and 91.0%, respectively). One year post-injection 3, the percentage of subjects seropositive remained high as compared to post-injection 3 (72.0%). Two years post- injection 3, the percentage of subjects seropositive remained high (65.4%).

Overall, geometric means of titres (GMTs) at baseline were comparable across serotypes with a trend to higher GMTs for serotype 2. GMTs ranged from 25.3 (1/dil) for serotype 4 to 55.3 (1/dil) for serotype 2 in the CYD Dengue Vaccine Group and from 26.2 (1/dil) for serotype 4 to 62.1 (1/dil) for serotype 2 in the Control Group.

Immunogenicity according to country

At baseline, in the CYD Dengue Vaccine Group, GMTs (1/dil) ranges were lower in Malaysia (from 14.7 for serotype 4 to 26.3 for serotype 2), Thailand (from 22.6 for serotype 4 to 41.5 for serotype 2), and Vietnam (from 13.9 for serotype 4 to 25.8 for serotype 2) as compared to Indonesia (from 51.5 for serotype 4 to 114 for serotype 2) and the Philippines (from 35.3 for serotype 4 to 105 for serotype 2), reflecting background incidence of serotypes and disease. One year post-injection 3, GMTs were still higher as compared to baseline for all serotypes and for all countries. Two years post-injection 3, GMTs were still higher as compared to baseline for all serotypes and for all countries.

Immunogenicity according to age

In the CYD Dengue Vaccine Group, GMTs at baseline, after the second and the third injection tended to be higher with age. Two years post-injection 3, GMTs were still higher as compared to baseline for all serotypes and for all age groups. The levels of GMTs decreased two years post-injection 3 as compared to one year post-injection 3 across age groups for the respective serotypes in the CYD Dengue Vaccine Group.

Immunogenicity according to dengue baseline

In the CYD Dengue Vaccine Group, GMTs per serotype post-injection 2 and post-injection 3 were higher in dengue immune subjects at baseline as compared to dengue non-immune subjects at baseline.

7.3. Other efficacy studies

7.3.1. Study CYD23

Phase IIb PoC Efficacy Study: CYD23. A total of 4002 subjects were evaluated at a single site in Thailand. This study was conducted between March 2012 and September 2013. Study CYD23 was a randomised, observer blind, controlled, monocentre, Phase IIb trial in 4002 subjects aged 4-11 years in Thailand. There were 3 injections and 2 groups of subjects:

- CYD dengue 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 in Cohort 2).

Two-step approach for enrolment:

- Step 1: The first 150 subjects (Cohort 1) received their first injection (100 received the dengue vaccine and 50 received the rabies vaccine) and were followed for safety up to 14 days
  - An Independent Data Monitoring Committee (IDMC) reviewed Day (D) 14 safety data
  - The IDMC and sponsor's recommendation to proceed with the inclusion of Cohort 2 and with the second injection of Cohort 1 was submitted to the Ethics Committee (EC) for consideration, along with the safety data from the first cohort.
- Step 2: Once approval had been obtained from the EC, Cohort 2 (n = 3852) was enrolled.

7.3.1.1. Follow-up of dengue cases

The active detection of dengue cases (that is, the Active Phase) started from the first injection until all subjects had been followed for at least 13 months after the third injection, on the condition that at least 27 cases of VC dengue had been detected and included in the per-protocol analysis set for Efficacy (PPSE). Beyond this time point, the detection of hospitalised dengue cases up to 5 years after the last injection in addition to fatal and related SAEs is done through Study CYD57.

The primary objective was to assess the efficacy of dengue vaccine after three injections in preventing symptomatic VC dengue cases, regardless of the severity, due to any of the four serotypes in children aged 4 to 11 years at the time of inclusion.

Safety data was also collected for 6 months after the last injection. Subjects were vaccinated at 0, 6, and 12 months. CYD Dengue Vaccine (Phase II lot). Each 0.5 mL reconstituted dose of tetravalent dengue vaccine contains: 5 ± 1 $\log_{10}$ cell-culture infectious dose 50% of each live, attenuated, dengue serotype 1, 2, 3, 4 virus. The control product 1 was Rabies vaccine (Verorab) reconstituted according to instructions and control product 2 was placebo (NaCl 0.9%).

7.3.1.2. Inclusion criteria

- Aged 4 to 11 years on the day of inclusion.
- Subject in good health, based on medical history and physical examination.
- Provision of assent form signed by the subject (for subjects ≥ 7 years old) and informed consent form signed by the parent or another legally acceptable representative.
- Subject and parent/legally acceptable representative able to attend all scheduled visits and to comply with all trial procedures.
- Subject attending one of the schools involved in the trial and living in the Ratchaburi Province.
- For a female subject of child-bearing potential (girls post-menarche), avoid becoming pregnant (use of an effective method of contraception or abstinence) for at least 4 weeks prior to first vaccination, until at least 4 weeks after the last vaccination.

7.3.1.3. Exclusion criteria

- Febrile illness (temperature ≥ 37.5°C) or moderate or severe acute illness/infection on the day of vaccination.
- For a female subject of child-bearing potential (girls post-menarche), known pregnancy or positive urine pregnancy test on the day of the first trial vaccination.
- Personal or family history of thymic pathology or myasthenia.
- Planned participation in another clinical trial during the present trial period.
- Known or suspected congenital or acquired immunodeficiency, immunosuppressive therapy such as anti-cancer chemotherapy or radiation therapy, or long-term systemic corticosteroids therapy.
- Known systemic hypersensitivity to any of the vaccine components or history of a life-threatening reaction to the trial vaccines or to a vaccine containing any of the same substances.
- Chronic illness at a stage that could interfere with trial conduct or completion.
- Receipt of blood or blood derived products in the past 3 months.
- Subject deprived of freedom by an administrative or court order.
- Participation in another clinical trial investigating a vaccine, drug, medical device, or a medical procedure in the 4 weeks preceding the first trial vaccination.
- Receipt of any vaccine in the 4 weeks preceding the first trial vaccination.
- Planned receipt of any vaccine in the 4 weeks following the first trial vaccination.
- Subject who planned to attend another school (outside the trial area) or move to another city in the coming 30 months.

7.3.1.4. Statistical methods

Two statistical analyses were performed for this trial:

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

7.3.1.5. Results

A total of 4014 subjects were screened from which 4002 were enrolled and randomised (2669 subjects in the dengue group and 1333 subjects in the control group); 150 subjects were enrolled and randomised in Cohort 1 (100 subjects in the dengue group and 50 subjects in the control group) and 3852 subjects in Cohort 2 (2569 subjects in the dengue group and 1283 subjects in the control group).

The vast majority of subjects (95.7% of all subjects) present at V01 completed the Active Phase of the study. Approximately 96% subjects were included in the FASE and approximately 92% were included in the PPSE. Failure to receive 3 injections and injection received outside the protocol defined time windows were the most common reasons for exclusion from the PPSE.

7.3.1.6. Demographic characteristics

Overall, there were slightly more female (51.8%) than male subjects (48.2%) and the mean age was 8.17 years. All demographic characteristics were similar in both treatment groups in the biological, immunological and reactogenicity subsets.

7.3.1.7. Efficacy

Primary Objective

After 3 injections of CYD dengue vaccine, the overall VE estimate was 30.2% (95% CI: -13.4, 56.6); the level of significance was not reached. A total of 78 VC dengue episodes were observed in 77 subjects after the completion of the 3 injections. Although this was more than the original estimate of 27 VC dengue cases, both the higher than estimated attack rate of dengue and a VE estimate that was lower than the 70% assumption resulted in the observed vaccine efficacy that did not reach statistical significance.

Secondary objectives

VE against severe VC dengue

Considering both WHO 1999 and IDMC severity assessments, a total of 5 severe VC dengue cases were identified during the Active Phase. Three were severe according to both WHO and IDMC severity assessments (1 in the dengue group and 2 in the control group. Moreover, there were no increases in the classic clinical signs of dengue such as bleeding, plasma leakage, or thrombocytopenia in vaccinees compared to controls. In conclusion, these results showed no increase of severe VC dengue in vaccinees as compared to controls.

Duration of clinical syndrome and hospitalisation

Independently from the number of cases observed in each group, there were no differences between vaccinees and controls with regard to the rate of hospitalisation or the duration of fever, clinical syndrome or hospitalisation. This demonstrates that breakthrough dengue infection in vaccinees was not clinically more severe than that observed in control subjects. There is no evidence of any enhanced disease in vaccinees infected with dengue.

Overall, baseline GMTs were similar across serotypes for both treatment groups: baseline GMTs ranged from 28.1 (1/dil) to 56.8 (1/dil) in the dengue group and from 23.2 (1/dil) to 43.7 (1/dil) in the control group. Increases in GMTs were observed after the first and second injections. With the exception of serotype 3, the third injection was not associated with further increases in GMTs; after the first, second, and third injection.

Baseline seropositivity rates against each serotype were similar across serotypes for both treatment groups (ranged from 54.8% to 60.4% in the dengue group and from 45.5% to 58.2% in the control group). Seropositivity rates against each serotype increased after the first and second injections of CYD dengue vaccine, and were > 90% 28 days after the second injection. One year after the third injection of CYD dengue vaccine, the seropositivity rates remained > 85% against each serotype.

Baseline seropositivity rates against at least 1, 2, 3 or all 4 serotypes were similar in both treatment groups and were in dengue versus control group approximately 70% versus 69%, 58% versus 55%, 56% versus 49%, and 46% versus 35%, respectively. Seropositivity rates against all 4 serotypes increased to > 90% after the second injection and remained high after the third injection. One year after the third injection of CYD dengue vaccine, the seropositivity rates remained > 80% against all 4 serotypes.

In this study, the primary estimate of VE was lower than anticipated and was not significant. This result was driven primarily by the finding that most of the serotypes identified were serotype 2 (32 VCD cases in the dengue group and 19 VCD cases in the control group were due

to serotype 2) for which the vaccine is least effective. The main clinically important outcome of this study was that there was no increase in severe VC in the vaccinated group.

7.3.2. Study CD12

Study CD12 was a Phase II Study in Adults in the US, Immunogenicity and Safety of Three Tetravalent Formulations of Dengue Vaccine Candidates in Healthy Adults Aged 18 to 45 Years in the US

7.3.2.1. Study objectives and design

The main objectives were to describe the safety and the humoral immune response against dengue after each injection of the 3 formulations of the CYD dengue vaccine. Study CYD12 was a randomised, double-blind Phase II study conducted in 5 centres in the USA. A total of 260 healthy adult subjects (18 to 45 years) were randomised into 3 groups: 104 subjects were to receive 3 injections, 6 months apart, of the final formulation (5555) of the CYD dengue vaccine, and 103 and 53 subjects were to receive different formulations of the CYD dengue vaccine, that is, 5553 and 4444, respectively.

The statistical analysis was descriptive.

7.3.2.2. Disposition

Among the 104 subjects randomised to receive the final formulation of the CYD dengue vaccine, all received the first injection, 86 received the second injection and 79 received the third injection.

7.3.2.3. Humoral immune response

At baseline in the Dengue Group receiving the final formulation, dengue GMTs and seropositivity rates against each serotype were low.

Dengue GMTs and seropositivity rates against serotypes 1, 2 and 3 progressively increased after each injection, while for serotype 4 the GMT markedly increased after the first injection (438 (1/dil)) and then decreased after the subsequent injections. PD3 GMTs ranged from 24.4 (1/dil) for serotype 1 to 133 (1/dil) for serotype 4. After the third injection of the CYD dengue vaccine, more than 71% of subjects were seropositive against each serotype considered separately and 62.9% of subjects were seropositive against all 4 serotypes.

7.3.2.4. Conclusion

The safety profile of the CYD dengue vaccine was satisfactory in this dengue non-immune population. Overall, the immune response progressively increased after each injection of the final formulation of the CYD dengue vaccine. After the third injection, 62.9% of subjects were seropositive against all 4 serotypes.

7.3.3. Study CYD51

Study CYD51 was a Phase II Different Schedules Study in Adults in the US, Evaluation of the Immune Response to Different Schedules of a Tetravalent Dengue Vaccine Administered With or Without Yellow Fever Vaccine in US Adults

7.3.3.1. Study objectives and design

The primary objectives were to describe the humoral immune response of the CYD dengue vaccine after the third injection and 6 month after the third injection with different vaccination schedules (0, 6, 12 or 0, 2, 6 months). The secondary objectives were to describe the humoral immune response and the safety of the CYD dengue vaccine after each injection with different vaccination schedules, and to describe the impact of previous vaccination against YF on the CYD dengue vaccine humoral immune response. Study CYD51 was a randomised, open label, Phase II study in 6 centres in the US. A total of 390 healthy adults (18 to 45 years) were randomised into 4 groups: 120 subjects were to receive 3 injections, 6 months apart, of the CYD dengue vaccine;

120 subjects were to receive 3 injections, at 0, 2 and 6 months, of the CYD dengue vaccine. In each of these groups, half of the subjects received YF vaccine 3 months to 10 years before the administration of the CYD dengue vaccine. In addition, 120 subjects were to receive the YF vaccination concomitantly with the first injection of the CYD dengue vaccine, and 2 subsequent injections at 2 and 6 months of the CYD dengue vaccine; and 30 subjects were to receive the YF vaccination only.

The statistical analysis was descriptive.

7.3.3.2. Disposition

Among the 120 subjects randomised to receive the CYD dengue vaccine with the 0, 6, 12 months schedule, 120 subjects received the first injection, 105 subjects received the second injection and 98 subjects received the third injection.

7.3.3.3. Humoral immune response

In the group co-administered, that is, receiving the CYD dengue vaccine with a 0, 2, 6 months schedule, the CYD dengue vaccine did not impact the YF immune response.

At baseline in the group receiving the CYD dengue vaccine with the 0, 6, 12 months schedule, dengue GMTs and seropositivity rates against each serotype were low Dengue GMTs and seropositivity rates against each serotype increased mainly after the first and second injections, then decreased or remained stable after the third injection. PD3 GMTs ranged from 14.8 (1/dil) for serotype 1 to 66.8 (1/dil) for serotype 4. After the third injection of the CYD dengue vaccine, more than 52% of subjects were seropositive against each serotype considered separately and 50.0% of subjects were seropositive against all 4 serotypes.

7.3.3.4. Conclusion

The safety profile of the CYD dengue vaccine was satisfactory in this dengue non-immune population. Overall, the immune response mainly increased after the first and second injection of the CYD dengue vaccine. After the third injection, 50.0% of subjects were seropositive against all 4 serotypes.

7.3.4. Study CYD17

Study CYD17 was a Phase III Lot-to-Lot Consistency Study in Adults in Australia, Lot-to-Lot Consistency and Bridging Study of a Tetravalent Dengue Vaccine in Healthy Adults in Australia

7.3.4.1. Study objectives and design

The primary objective was to demonstrate that the 3 different Phase III lots of the CYD dengue vaccine induced an equivalent immune response after the third injection in terms of GMT for each serotype (lot consistency). The secondary objectives were to demonstrate that Phase II and pooled Phase III lots of the CYD dengue vaccine (bridging) induced an equivalent immune response after the third injection in terms of GMT for each serotype and to describe the immunogenicity after the third injection and the safety after each injection. Study CYD17 was a randomised, blind observer, controlled lot-to-lot Phase III study conducted in 8 centres in Australia. A total of 715 healthy adult subjects (18 to 60 years) were randomised into 5 groups: 3 groups of 165 subjects were to receive 3 injections, 6 months apart, of 1 of the 3 Phase III lots of the CYD dengue vaccine, 165 subjects were to receive 3 injections, 6 months apart, of one Phase II lot of the CYD dengue vaccine and 55 subjects were to receive 3 injections, 6 months apart, of a placebo.

For the statistical analysis, an equivalence testing approach was used to compare GMTs 28 days after the third injection, between each pair of Phase III lots for each serotype. Equivalence among the 3 lots was established if equivalence was demonstrated for all serotypes. Once lot-to-lot consistency had been established, the immunogenicity of the Phase III lots (pooled data) was compared to that of the Phase II lot using an equivalence testing approach.

7.3.4.2. Disposition

Among the 715 randomised subjects: 712 subjects received the first injection, 649 received the second injection and 619 received the third injection, regardless of the treatment groups.

7.3.4.3. Lot-to-lot consistency

Equivalence of the GMTs 28 days after the third injection was statistically demonstrated in the PP Analysis Set for each pair of lots for each serotype (11/12 comparisons) except for serotype 2 (Lot 1-Lot 2) where the upper limit of the 95% CI was 0.340; that is, higher than the pre-defined limit of 0.301. Although one statistical comparison failed, the Phase III lots can be considered as clinically consistent. Compared to the Phase II lot, the level of GMTs 28 days after the third injection was clinically similar for serotypes 1, 3, and 4 and was higher for serotype 2 in the pooled Phase III lots.

7.3.4.4. Humoral immune response

At baseline, 2.4% and 6.6% of subjects in pooled Dengue Group were FV and dengue immune, respectively; 5.3% and 8.8% of subjects in the Control Group, were FV and dengue immune, respectively. At baseline, dengue GMTs and seropositivity rates against each serotype were comparable in the two treatment groups.

In the Control Group, dengue GMTs and seropositivity rates against each serotype did not appreciably change after the third injection. In the Dengue Group, PD3 GMTs were higher against serotype 3, 4 and 2 compared to serotype 1, ranging from 45.3 (1/dil) for serotype 2 to 111 (1/dil) for serotype 4, compared to 18 (1/dil) for serotype 1. After the third injection of the CYD dengue vaccine, more than 62% of subjects were seropositive against each serotype considered separately and 54.1% of subjects were seropositive against all 4 serotypes.

7.3.4.5. Conclusion

The overall safety profile of the CYD dengue vaccine lots was consistent and satisfactory in this dengue non-immune population as compared to placebo, and was similar between Phase II and Phase III lots. Overall, the immune response was consistent across Phase III and Phase II lots. After the third injection, 54.1% of subjects were seropositive against all 4 serotypes. Study ID

7.3.5. Study CYD22

Study CYD22 was a Phase II Study in Adults, Adolescents and Children in Vietnam, Immunogenicity and Safety of Tetravalent Dengue Vaccine in Healthy Subjects Aged 2 to 45 Years in Vietnam

7.3.5.1. Study objectives and design

The objectives were to describe the humoral immune response and the safety of the CYD dengue vaccine after each injection in the 4 age cohorts. Long-term persistence of Ab levels was also evaluated up to 4 years after the third injection.

Study CYD22 was a randomised, blind observer, controlled Phase II study conducted in 1 centre in Vietnam. A total of 180 healthy subjects, adults (18 to 60 years), adolescents (12 to 17 years) and children (2 to 5 and 6 to 11 years) were sequentially enrolled in 2 groups: 120 subjects were to receive 3 injections, 6 months apart, of the CYD dengue vaccine and 60 subjects were to receive one injection of a meningococcal polysaccharide vaccine A+C, then one injection of a placebo (sodium chloride containing human serum albumin) at 6 months and one injection of Vi typhoid polysaccharide vaccine (Typhim Vi) at 12 months.

The statistical analysis was descriptive.

7.3.5.2. Disposition

All 180 randomised subjects received the first injection, 174 subjects received the second injection and 172 subjects received the third injection, regardless of the treatment groups. A total of 166 subjects completed the 4 year follow-up.

7.3.5.3. Humoral immune response and persistence of Ab levels

At baseline, 77.2% of subjects were FV immune (75.8% in the Dengue Group and 80.0% in the Control Group), 38.9% of subjects were dengue immune (39.2% in the Dengue Group and 38.3% in the Control Group) and 38.5% of subjects were JE immune (37.0% in the Dengue Group and 41.7% in the Control Group). At baseline, dengue GMTs and seropositivity rates against each serotype were comparable in the two treatment groups.

In the Control Group, dengue GMTs and seropositivity rates against each serotype did not appreciably change following each injection and during the 4 years of follow-up. In the Dengue Group, dengue GMTs against each serotype increased after each injection of the CYD dengue vaccine. PD3 GMTs ranged from 129 (1/dil) for serotype 1 to 216 (1/dil) for serotype 2. GMTRs PD3/baseline were not calculated. After the third injection of the CYD dengue vaccine, more than 93% of subjects were seropositive against each serotype considered separately and 92.1% of subjects were seropositive against all 4 serotypes.

During the 4 years of follow-up after the third injection, dengue GMTs and seropositivity rates against each serotype slightly decreased each year. At Year 4, dengue GMTs were 1.3 to 2.2-fold above baseline, and seropositivity rates against each serotype were higher than baseline, ranging from 61.6% for serotype 1 to 76.8% for serotype 4.

7.3.5.4. Subpopulation analyses

Dengue GMTs levels tended to be higher with increasing age for all serotypes at baseline and after each injection, although this was less marked for serotype 3.

7.3.5.5. Conclusion

The safety profile of the CYD dengue vaccine was satisfactory, with decreasing systemic reactogenicity after subsequent injections. After the third injection, 92.1% of subjects were seropositive against all 4 serotypes. Although the dengue baseline seropositivity rates and GMTs differed between the age groups (that is, lowest in children and highest in adults), GMTs against each serotype increased in all age groups following 3 injections of the CYD dengue vaccine, with the greatest increase observed in the children (2 to 5 years) and children (6 to 11 years). Although the GMT levels declined over time, they were higher than baseline levels 4 years after the third injection.

7.3.6. Study CYD28

Study CYD28 was a Phase II Study in Adults, Adolescents and Children in Singapore, Immunogenicity and Large-Scale Safety of Tetravalent Dengue Vaccine in Healthy Subjects Aged 2 to 45 Years in Singapore

7.3.6.1. Study objectives and design

The primary objectives were to describe the safety in all subjects and the humoral immune response in a subset of subjects in the Dengue Group after each injection in the 3 age cohorts. The secondary objective was to evaluate long-term persistence of Ab levels up to 4 years after the third injection. The cellular immune response was also evaluated after the first and third injections and up to 4 years after the third injection.

Study CYD28 is a randomised, blind observer for the first injection and single-blind for the second and the third injections, controlled Phase II study in 5 centres in Singapore. A total of 1198 healthy children, adolescents and adults were randomised into 2 groups: 898 subjects were to receive 3 injections, 6 months apart, of the CYD dengue vaccine, and 300 subjects were

to receive one injection of a placebo for the first injection, then children < 12 years received 2 injections of a hepatitis A vaccine (Havrix) at 6 and 12 months and adolescents ≥ 12 years received 2 injections of an influenza vaccine (Vaxigrip) at 6 and 12 months.

The statistical analysis was descriptive.

All 1198 randomised subjects received the first injection, 1146 subjects received the second injection and 1118 subjects received the third injection, regardless of the treatment groups. A total of 1046 subjects completed the 4 year follow-up.

7.3.6.2. Humoral immune response and persistence of Ab levels (subset of 585 subjects)

At baseline, 27.5% of subjects were dengue immune: 26.0% in the Dengue Group and 32.0% in the Control Group. About 50% of the adults (18 to 45 years) were dengue immune at baseline compared with 14% to 20% of the adolescents (12 to 17 years) and children (2 to 11 years).

At baseline, dengue GMTs and seropositivity rates against each serotype were comparable in the two treatment groups.

In the Control Group, dengue GMTs and seropositivity rates against each serotype did not appreciably change following each injection or during the 3 years of follow-up. In the Dengue Group, dengue GMTs against each serotype increased after each injection of the CYD dengue vaccine. PD3 GMTs ranged from 46.6 (1/dil) for serotype 1 to 100 (1/dil) for serotype 3, with GMTRs PD3/baseline ranging from 3.31 for serotype 1 to 8.13 for serotype 4. After the third injection of the CYD dengue vaccine, more than 79% of subjects were seropositive against each serotype considered separately and 66.7% of subjects were seropositive against all 4 serotypes. During the 4 years of follow-up after the third injection, dengue GMTs against each serotype decreased each year. At Year 4, dengue GMTs were 1.2 to 3.2 fold above baseline.

7.3.6.3. Subpopulation analysis

Dengue GMTs tended to be higher in adults compared to adolescents and children for all serotypes at baseline and after each injection. For all serotypes, the GMTR tended to be higher in children after the third injection.

The humoral immune response to recent dengue field isolates at inclusion and after the second and third vaccinations was evaluated in a subset of subjects. Results showed that the human sera Abs induced by the CYD dengue vaccine cross-reacted against geographically diverse strains of different genotypes.

NS3-specific and CYD-specific responses slightly decreased one year after the third injection, the latter response being more pronounced with only IFNγ levels remaining above quantification limits. This persistent dominance of IFNγ over TNFα and interleukin 13 (IL-13), and other helper T cell (Th) 2 cytokines, is observed in mild disease as opposed to the pro-inflammatory cytokines observed in severe disease. Overall, the profile was unchanged 1 year after the third injection and up to 4 years. However, further quantitative decreases were observed 2 and 3 years after the third injection with a stabilisation 4 years after the third injection, in both NS3 specific and DEN specific responses, which remained dominated by IFNγ. DEN NS3 specific responses boosted by the first injection of the CYD dengue vaccine also remained detectable, but again with some further decline after 4 years.

7.3.6.4. Conclusion

The safety profile of the CYD dengue vaccine was satisfactory, with a decreasing systemic reactogenicity after subsequent injections. After the third injection, 66.7% of subjects were seropositive against all 4 serotypes. Although the baseline seropositivity rates and GMTs against each serotype differed between the age groups (that is, lower in children and adolescents compared to adults), GMTs increased in all age groups following 3 injections of the CYD dengue vaccine, with the greatest increase observed in the children (2 to 11 years). Although the GMT

levels declined over time, they were higher than baseline levels and were still detected in a high number of vaccinated subjects for both humoral and cellular responses 4 years after the third injection.

7.3.7. Study CYD47

Study CYD47 was a Phase II Study in Adults in India, Immunogenicity and Safety of a Tetravalent Dengue Vaccine in Healthy Adult Subjects Aged 18 to 45 Years in India

7.3.7.1. Study objectives and design

The primary objective was to describe the humoral immune response and the safety of the CYD dengue vaccine after each injection. Study CYD47 was a randomised, blind observer, controlled Phase II study conducted in 5 centres in India. A total of 189 healthy adults (18 to 45 years) were randomised into 2 groups: 128 subjects were to receive 3 injections, 6 months apart, of the CYD dengue vaccine and 61 subjects were to receive 3 injections, 6 months apart, of a placebo.

The statistical analysis was descriptive.

7.3.7.2. Disposition

Among the 189 randomised subjects, 188 received the first injection, 175 received the second injection and 172 received the third injection, regardless of the treatment groups.

7.3.7.3. Humoral immune response

At baseline, 90.4% of subjects were FV immune (89.7% in the Dengue Group and 91.8% in the Control Group), and 87.2% of subjects were dengue immune (86.5% in the Dengue Group and 88.5% in the Placebo Group). At baseline, dengue GMTs and seropositivity rates against each serotype were high in the two treatment groups and were comparable.

In the Control Group, dengue GMTs and seropositivity rates against each serotype did not appreciably change following each injection. In the Dengue Group, dengue GMTs and seropositivity rates for each serotype markedly increased after the first injection. GMTs against each serotype tended to decrease slightly after the second and third injections. PD3 GMTs ranged from 336 (1/dil) for serotype 4 to 709 (1/dil) for serotype 3 with GMTRs PD3/baseline ranging from 2.38 for serotype 2 to 6.11 for serotype 4. After the third injection of the CYD dengue vaccine, more than 97% of subjects were seropositive against each serotype considered separately and 97.4% of subjects were seropositive against all 4 serotypes.

7.3.7.4. Conclusion

The safety profile of the CYD dengue vaccine was satisfactory, with a decreasing systemic reactogenicity after subsequent injections. After the third injection, 97.4% of subjects were seropositive against all 4 serotypes.

7.3.8. Study CYD08

Study CYD08 was a Phase II Study on Toddlers in the Philippines, Immunogenicity and Safety of CYD Dengue Vaccine in Healthy Toddlers Aged 12 to 15 Months in the Philippines

7.3.8.1. Study objectives and design

The primary objectives were to describe the safety of the CYD dengue vaccine after each injection, with the first injection administered alone or concomitantly with the MMR vaccine; and to describe the vaccinal viremia and biological safety after the first injection of the CYD dengue vaccine. The secondary objectives were to describe the humoral immune response of the CYD dengue vaccine after each injection and of the MMR vaccine.

Study CYD08 was a randomised, controlled, modified double-blind for the first injection and open-label for the second and third injections, Phase II study conducted in 2 centres in the Philippines. A three-step approach to enrolment in 3 cohorts was performed for safety

purposes. In total, 210 healthy toddlers (12 to 15 months old) were randomised into 4 groups: 60 subjects were to receive the MMR vaccine one month before, followed by 3 injections, 6 months apart, of the CYD dengue vaccine (Group 1); 30 subjects were to receive the MMR vaccine one month before, followed by 1 injection of a control vaccine against varicella and 2 injections at 6 and 12 months of a control vaccine against hepatitis A (Group 2); 60 subjects were to receive a control vaccine against varicella one month before, followed by the first CYD dengue vaccine injection co- administered with the MMR vaccine, and the 2 subsequent injections of the CYD dengue vaccine at 6 and 12 months (Group 3); and 60 subjects were to receive the MMR vaccine one month before, followed by the first injection of the CYD dengue vaccine co-administered with a placebo, and the 2 subsequent injections of the CYD dengue vaccine at 6 and 12 months.

The statistical analysis was descriptive.

7.3.8.2. Disposition

Among the 210 randomised subjects, 209 subjects received the first injection, 208 subjects received the second injection and 205 subjects received the third injection, regardless of the cohorts and treatment groups.

7.3.8.3. Co-administration

The co-administration of MMR with the first injection of the CYD dengue vaccine had no impact on the immune response of MMR induced a reduction of the immune response to the first injection of the CYD dengue vaccine had no impact on the immune response of the CYD dengue after 3 injections.

7.3.8.4. Humoral immune response

At baseline, 48.9% of subjects in the Dengue Group and 53.6% in the Control Group were FV immune, 7.9% of subjects in the Dengue Group and 10.3% of subjects in the Control Group were JE immune; and 44.1% of subjects in the Dengue Group and 44.8% of subjects in the Control Group were dengue immune. At baseline, dengue GMTs and seropositivity rates against each serotype were comparable in the two treatment groups.

In the Control Group, dengue GMTs and seropositivity rates against each serotype did not change following the third injection, although a trend to a slight increase was observed after the second injection: GMTRs PD3/baseline ranged from 1.17 for serotype 4 to 2.16 for serotype 1.

In the Dengue Group, dengue GMTs against each serotype increased after each injection. After the third injection, PD3 GMTs ranged from 112 (1/dil) for serotype 1 to 351 (1/dil) for serotype 3, with GMTRs PD3/baseline ranging from 18.9 for serotype 1 to 28.2 for serotype 3. After the third injection of the CYD dengue vaccine, more than 95% of subjects were seropositive against each serotype considered separately and 93.7% of subjects were seropositive against all 4 serotypes.

7.3.8.5. Conclusion

The safety profile of the CYD dengue vaccine was satisfactory, with a decreasing systemic reactogenicity after the second injection. The co-administration of the CYD dengue vaccine and the MMR vaccine did not show any impact on the immune response for the MMR vaccine or for the CYD dengue vaccine following the 3-injection regimen. After the third injection, 93.7% of subjects were seropositive against all 4 serotypes.

7.3.9. Study CYD32

Study CYD32 was a Phase III Study in Children in Malaysia, Safety and Immunogenicity of a Tetravalent Dengue Vaccine in Healthy Children Aged 2 to 11 Years in Malaysia.

7.3.9.1. Study objectives and design

The primary objectives were to describe the safety of the CYD dengue vaccine after each injection and the humoral immune response after the second and third injections in the 2 age cohorts. Study CYD32 was a randomised, blind observer, controlled Phase III study conducted in 4 sites in Malaysia. A total of 250 healthy children (2 to 5 and 6 to 11 years) were randomised into 2 groups: 199 subjects were to receive 3 injections, 6 months apart, of the CYD dengue vaccine and 51 subjects were to receive 3 injections, 6 months apart, of a placebo.

The statistical analysis was descriptive.

7.3.9.2. Disposition

Among the 250 randomised subjects, all subjects received the first injection, 247 subjects received the second injection and 246 subjects received the third injection, regardless of the treatment groups.

7.3.9.3. Humoral immune response

At baseline, 55.6% and 62.0% of subjects were FV immune in the Dengue Group and in the Control Group, respectively, and 44.9% and 48.0% of subjects were dengue immune in the Dengue Group and in the Control Group, respectively. At baseline, dengue GMTs and seropositivity rates against each serotype were comparable in the two treatment groups.

In the Control Group, dengue GMTs and seropositivity rates against each serotype did not appreciably change following the second and third injections. In the Dengue Group, dengue GMTs against each serotype sharply increased after the second injection. Dengue GMTs slightly increased or remain stable after the third injection of the CYD dengue vaccine. PD3 GMTs ranged from 114 (1/dil) for serotype 4 to 193 (1/dil) for serotype 3, with GMTRs PD3/baseline ranging from 6.11 for serotype 1 to 7.96 for serotype 3. After the third injection of the CYD dengue vaccine, more than 96% of subjects were seropositive against each serotype considered separately and 91.8% of subjects were seropositive against all 4 serotypes.

7.3.9.4. Conclusion

The safety profile of the CYD dengue vaccine was satisfactory, with decreasing systemic reactogenicity after subsequent injections. After the third injection, more than 96% of subjects were seropositive against each serotype. A trend toward higher GMTs was noted in older subjects.

7.3.10. Study CYD13

Study CYD13 was a Phase II Study in Children and Adolescents in Colombia, Honduras, Mexico and Puerto Rico, Immunogenicity and Safety of Sanofi Pasteur's CYD Dengue Vaccine in Healthy Children and Adolescents Aged 9 to 16 Years in Latin America

7.3.10.1. Study objectives and design

The primary objectives were to describe the humoral immune response and the safety of the CYD dengue vaccine after each injection. Study CYD13 was a randomised, blind observer for the first and second injections, controlled Phase II study conducted in 5 centres located in Colombia, Honduras, Mexico and Puerto Rico. A total of 600 healthy children and adolescents (9 to 16 years) were randomised into 2 groups: 401 subjects were to receive 3 injections, 6 months apart, of the CYD dengue vaccine and 199 subjects were to receive 2 injections, 6 months apart, of a placebo and a third injection, 6 months apart, of a tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed (Adacel).

The statistical analysis was descriptive.

7.3.10.2. Disposition

All 600 randomised subjects received the first injection, 558 subjects received the second injection and 544 subjects received the third injection, regardless of the treatment groups.

7.3.10.3. Humoral immune response

At baseline, 79.3% of subjects were FV immune (78.8% in the Dengue Group and 80.4% in the Control Group), 76.0% of subjects were dengue immune (75.1% in the Dengue Group and 77.9% in the Control Group) and 71.2% of subjects were YF immune (70.1% in the Dengue Group and 73.4% in the Control Group). At baseline, dengue GMTs and seropositivity rates against each serotype were high in the two treatment groups and were comparable.

In the Control Group, dengue GMTs and seropositivity rates against each serotype did not appreciably change following each injection.

In the Dengue Group, dengue GMTs against serotypes 1 and 3 progressively increased after each injection. For serotype 2, GMTs progressively increased after the first and second injection and then slightly decreased after the third injection. For serotype 4, GMTs markedly increased after the first injection (416 (1/dil)) and then decreased after the subsequent injections. PD3 GMTs ranged from 273 (1/dil) for serotype 4 to 594 (1/dil) for serotype 3, with GMTRs PD3/baseline ranging from 3.16 for serotype 1 to 5.47 for serotype 4. After the third injection, more than 94% of subjects were seropositive against each serotype considered separately and 93.4% of subjects were seropositive against all 4 serotypes.

7.3.10.4. Subpopulation analyses

Dengue GMTs against each serotype tended to be lower in the younger cohort (9 to 11 years) at baseline and after each injection compared to the older cohort (12 to 16 years). Except for serotype 1, GMTRs were usually higher in the younger cohort after each injection.

The humoral immune response to recent dengue field isolates at inclusion and after the second and third vaccinations was evaluated in a subset of subjects. Results showed that the human sera Abs induced by the CYD dengue vaccine cross-reacted against geographically diverse strains of different genotypes.

7.3.10.5. Conclusion

The safety profile of the CYD dengue vaccine was satisfactory, with decreasing reactogenicity after subsequent injections. After the third injection, 93.4% of subjects were seropositive against all 4 serotypes. The seropositivity rates against all 4 serotypes were high in both age groups but a trend to higher GMTs was noted in in older subjects.

7.3.11. Study CYD24

Study CYD24 was a Phase II Study in Children in Peru, Immunogenicity and Safety of a Tetravalent Dengue Vaccine in Healthy Children Aged 2 to 11 Years Previously Vaccinated Against Yellow Fever in Peru.

7.3.11.1. Study objectives and design

The main objectives were to describe the humoral immune response and the safety of the CYD dengue vaccine after each injection in the 2 age cohorts of YF-primed children. Study CYD24 was a randomised, blind observer, controlled Phase II study conducted in 1 centre in Peru. Children documented as having received a YF vaccine since at least 1 month before enrolment in the study were eligible. A total of 300 healthy children (2 to 5 and 6 to 11 years) were randomised into 2 groups: 200 subjects were to receive 3 injections, 6 months apart, of the CYD dengue vaccine and 100 subjects were to receive 2 injections, 6 months apart, of a placebo and 1 injection of a pneumococcal polysaccharide vaccine (Pneumo23) at 12 months.

The statistical analysis was descriptive.

7.3.11.2. Disposition

Among the 300 randomised subjects, 298 subjects received the first injection, 280 subjects received the second injection and 276 subjects received the third injection, regardless of the treatment groups.

7.3.11.3. Humoral immune response

At baseline, 81.4% and 83.8% of subjects were YF immune in the Dengue Group and in the Control Group, respectively, and 37.6% and 48.5% of subjects were dengue immune in the Dengue Group and in the Control Group, respectively. At baseline, dengue GMTs and seropositivity rates against each serotype were comparable in the two treatment groups.

In the Control Group, dengue GMTs and seropositivity rates against each serotype did not appreciably change following each injection, although a trend to a slight increase was observed after the third injection: GMTRs PD3/baseline ranged from 1.29 for serotype 2 to 1.99 for serotype 4. In the Dengue Group, dengue GMTs and seropositivity rates against each serotype sharply increased after the first and second injections of the CYD dengue vaccine. More than 94% of subjects were seropositive against each serotype after the second injection of the CYD dengue vaccine. GMTs against each serotype slightly increased after the third injection of the CYD dengue vaccine. PD3 GMTs ranged from 178 (1/dil) for serotype 2 to 190 (1/dil) for serotype 3, with GMTRs PD3/baseline ranging from 10.9 for serotype 1 to 23.5 for serotype 4. After the third injection, more than 96.0% of subjects were seropositive against each serotype considered separately and 94.1% of subjects were seropositive against all 4 serotypes.

7.3.11.4. Conclusion

The safety profile of the CYD dengue vaccine was satisfactory, with decreasing systemic reactogenicity after subsequent injections. A strong immune response was observed already after the second injection in this YF vaccinated population. The immune response was generally higher in the younger cohort.

7.3.12. Study CYD30

Study CYD30 was a Phase II Study in Children and Adolescents in Brazil, Immunogenicity and Safety of the CYD dengue vaccine in Healthy Children and Adolescents Aged 9 to 16 Years in Brazil.

7.3.12.1. Study objectives and design

The primary objectives were to describe the humoral immune response and the safety of the CYD dengue vaccine after each injection. Study CYD30 was a randomised, blind observer, controlled Phase II study conducted in 1 centre in Brazil. A total of 150 healthy children and adolescents (9 to 16 years) were randomised into 2 groups: 100 subjects were to receive 3 injections, 6 months apart, of the CYD dengue vaccine and 50 subjects were to receive 3 injections, 6 months apart, of a placebo.

The statistical analysis was descriptive.

7.3.12.2. Disposition

All 150 randomised subjects received the first injection, 141 subjects received the second injection and 136 subjects received the third injection, regardless of the treatment groups.

7.3.12.3. Humoral immune response

At baseline, 81.8% of subjects were FV immune (80.8% in the Dengue Group and 83.7% in the Control Group), 69.6% of subjects were dengue immune (68.7% in the Dengue Group and 71.4% in the Control Group) and 73.6% of subjects were YF immune (70.7% in the Dengue Group and 79.6% in the Control Group). At baseline, dengue GMTs and seropositivity rates against each serotype were high in the two treatment groups and were comparable.

In the Control Group, dengue GMTs and seropositivity rates did not appreciably change following each injection, although a trend to a slight increase was observed after the second injection. GMTRs PD3/baseline ranged from 1.24 for serotype 3 to 1.68 for serotype 2. In the Dengue Group, dengue GMTs and seropositivity rates for serotypes 1, 2 and 3 markedly increased after the first and second injections, while for serotype 4, GMTs markedly increased after the first injection but decreased after the second injection. More than 95% of subjects were seropositive against each serotype after the second injection of the CYD dengue vaccine. GMTs and seropositivity rates for serotypes 1, 2 and 3 decreased after the third injection, while for serotype 4, GMTs increased after the third injection. PD3 GMTs ranged from 267 (1/dil) for serotype 1 to 741 (1/dil) for serotype 3, with GMTRs PD3/baseline ranging from 4.92 for serotype 1 to 20.2 for serotype 4. After the third injection, more than 96% of subjects were seropositive against each serotype considered separately and 96.6% of subjects were seropositive against all 4 serotypes.

7.3.12.4. Subpopulation analyses

Dengue GMTs against each serotype tended to be lower in the younger cohort (9 to 11 years) than in the older cohort (12 to 16 years) at baseline and after each injection, although this was less marked for serotype 4. For all serotypes, the GMTR tended to be higher in the younger cohort after the second and third injections.

7.3.12.5. Conclusion

The safety profile of the CYD dengue vaccine was satisfactory, with a decreasing reactogenicity after subsequent injections. After the third injection, 96.6% of subjects were seropositive against all 4 serotypes. The seropositivity rates against all 4 serotypes were high in both age groups. A trend to higher GMTs against each serotype was noted in older subjects who had higher GMTs at baseline, reflecting increased exposure to natural dengue infection in the older age group.

7.3.13. Study CYD29

Study CYD29 was a Phase III Study in Toddlers in Colombia and Peru, Immunogenicity and Safety of Yellow Fever Vaccine (Stamaril) Administered Concomitantly with Tetravalent Dengue Vaccine in Healthy Toddlers at 12-13 Months of Age in Colombia and Peru.

7.3.13.1. Study objectives and design

The primary objective was to demonstrate the non-inferiority of the immune response against YF in FV non-immune subjects at baseline receiving 1 injection of Stamaril co-administered with the first injection of the CYD dengue vaccine compared to Stamaril co-administered with a placebo. Part of secondary objectives was to describe the humoral immune response of the CYD dengue vaccine after the second and third injection and the safety of the CYD dengue vaccine after each injection. Study CYD29 was a randomised, blind observer, Phase III study conducted in 1 centre in Colombia and 1 centre in Peru. A total of 792 healthy toddlers (12 to 13 months old) were randomised into 2 groups: 396 subjects were to receive the Stamaril concomitantly with the first injection of the CYD dengue vaccine, followed by 2 subsequent injections of the CYD dengue vaccine at 6 and 12 months; and 396 subjects were to receive the Stamaril concomitantly with placebo, followed by 2 injections of the CYD dengue vaccine at 6 and 12 months.

A non-inferiority test was performed using the 95% two-sided CI of the difference between the seroconversion rates against YF. Non-inferiority was demonstrated if the lower limit of the 95% CI was greater than -10%.

7.3.14. Disposition

Among the 396 subjects randomised in the group receiving 3 injections of the CYD dengue vaccine, 394 subjects received the first injection, 372 subjects received the second injection and 364 subjects received the third injection.

7.3.14.1. Non-inferiority

The non-inferiority on Stamaril was demonstrated with a 0.334 difference and a 95% CI of (-0.976; 1.87).

7.3.14.2. Humoral immune response (subset of 113 subjects)

At baseline, 14.2% of subjects were FV immune, 8.9% of subjects were YF immune and 6.0% of subjects were dengue immune. At baseline, dengue GMTs and seropositivity rates against each serotype were low.

Dengue GMTs and seropositivity rates against each serotype increased after the second injection, and slightly increased or remained similar after the third injection. PD3 GMTs ranged from 74.0 (1/dil) for serotype 4 to 181 (1/dil) for serotype 3, with GMTRs PD3/baseline ranging from 7.26 for serotype 4 to 18.0 for serotype 3. After the third injection, more than 97% of subjects were seropositive against each serotype considered separately and 97.3% of subjects were seropositive against all 4 serotypes.

7.3.14.3. Conclusion

The safety profile of the CYD dengue vaccine was satisfactory, with a decreasing reactogenicity after subsequent injections. The primary objective was met with the non-inferiority of Stamaril when co-administered with the first injection of the CYD dengue vaccine. The co-administration did not show any impact on the immune response for Stamaril or for the CYD dengue vaccine following a 3-injection regimen. After the third injection, 97.3% of subjects were seropositive against all 4 serotypes of dengue.

7.3.15. Study CYD33

Study CYD33 was a Phase III Study in Toddlers in Mexico, Immunogenicity and Safety of a Booster Injection of DTaP-IPV//Hib (PentaximTM) Administered Concomitantly with Tetravalent Dengue Vaccine in Healthy Toddlers Aged 15 to 18 Months in Mexico.

7.3.15.1. Study objectives and design

The primary objective was to demonstrate the non-inferiority of the immune response against diphtheria, tetanus, pertussis, polio and Hib antigens in subjects receiving one booster injection of the Pentaxim vaccine co-administered with the second injection of the CYD dengue vaccine compared to the Pentaxim vaccine co-administered with a placebo. Part of secondary objectives was to describe the humoral immune response of the CYD dengue vaccine after the second and third injection and the safety of the CYD dengue vaccine after each injection. CYD33 was a randomised, blind observer (for the second injection of the CYD dengue vaccine), open-label (for the first and third injection of the CYD dengue vaccine), Phase III study conducted in 3 centres in Mexico. A total of 624 healthy toddlers (9 to 12 months old) were randomised into 2 groups: 309 subjects were to receive 3 injections, 6 months apart, of the CYD dengue vaccine with a booster injection of the Pentaxim vaccine co-administered with the second injection and a placebo injection at 7 months; and 315 subjects were to receive 1 injection of the CYD dengue vaccine followed by a booster injection of the Pentaxim vaccine co-administered with a placebo at 6 months, followed by the second and third injection of the CYD dengue vaccine at 7 and 12 months.

A non-inferiority test was performed using the 95% two-sided CI of the between the seroprotection rates for each antigen. Non-inferiority was demonstrated if the lower limit of the 95% CI was greater than -10%.

7.3.15.2. Disposition

Among the 309 randomised subjects receiving the 3 injections of the CYD dengue vaccine at a 0, 6, 12 months schedule, 309 subjects received the first injection, 309 subjects received the second injection, and 298 subjects received the third.

7.3.15.3. Results

The non-inferiority was demonstrated for each antigen with a lower limit of the differences in the 95% CI ranging from -4.87 to -1.14.

7.3.15.4. Humoral immune response (subset of 109 subjects)

At baseline, 8.0% of subjects were dengue immune. Dengue GMTs and seropositivity rates against each serotype were low. Dengue GMTs and seropositivity rates against each serotype increased after the second injection, and slightly increased or remained similar after the third injection. PD3 GMTs ranged from 93.1 (1/dil) for serotype 1 to 196 (1/dil) for serotype 3, with GMTRs PD3/baseline ranging from 8.91 for serotype 1 to 19.1 for serotype 3. After the third injection, all subjects were seropositive against each serotype considered separately and against all 4 serotypes.

7.3.15.5. Conclusion

The safety profile of the CYD dengue vaccine was satisfactory, with a decreasing reactogenicity after the third injection. The primary objective was met with the non-inferiority of Pentaxim when co-administered with the second injection of the CYD dengue vaccine. The co-administration did not show any impact on the immune response for Pentaxim or for the CYD dengue vaccine following a 3-injection regimen. After the third injection, all subjects were seropositive against all 4 serotypes.

7.3.16. Evaluator commentary: other efficacy studies

There were multiple efficacy studies done, largely stepwise, in concordance with WHO and local safety recommendations. These were done initially in non-endemic and then in endemic regions, primarily to ensure that the vaccine was safe in terms of reactogenicity and in not exacerbating Dengue infection, and then assessing efficacy, initially in terms of GMTs and then also in terms of dengue infection prevention. Overall, these were well conducted studies (many already published) which showed efficacy, both serological and clinical without any impact on worsening of actual clinical cases of dengue. They paved the way for the large pivotal studies performed essentially in primary school aged children in endemic areas.

7.4. Analyses performed across trials: pooled and meta analyses

7.4.1. Meta-analysis of Studies CYD14/CYD15

These Phase III efficacy studies were powered to provide accurate VE estimates. As the outcome measures for efficacy were identical and the results from the 2 Phase III efficacy studies were highly consistent, an integrated efficacy analysis was produced to summarise the overall efficacy of the CYD dengue vaccine, and to improve the precision of the estimates for specific endpoints and analyses such as VE in preventing severe VCD cases, VE in preventing hospitalised VCD cases, and more generally VE in subpopulations where fewer cases were observed at the study.

7.4.2. VE against any serotype

Efficacy results obtained in Studies CYD14 and CYD15, and in the meta-analysis in the PPSE and in the FASE are presented in all subjects and in subjects from 9 years of age. In the Phase III studies, the primary endpoint was assessed in:

- 10,059 subjects aged 2 to 14 years in Study CYD14: 6709 subjects received 3 injections of the CYD dengue vaccine 6 month apart and were included in the PPSE.
- 18,834 subjects aged 9 to 16 years included in Study CYD15: 12,573 subjects received 3 injections of the CYD Dengue vaccine 6 month apart and were included in the PPSE.

Overall, when pooling the results from the two Phase III efficacy studies, efficacy in the PPSE was assessed in 19,282 subjects aged 2 to 16 years receiving 3 injections of the CYD dengue vaccine 6 months apart. In the meta-analysis, VE in preventing the occurrence of VCD due to any serotype from 28 days post-injection 3 to the end of the Active Phase was of 59.2% in the PPSE when pooling Studies CYD14 and CYD15, which was in the same range as VE estimates from individual studies. Similar results were observed in the FASE, including all VCD cases that occurred during the first 25 months of the study in all subjects having received at least one injection, with a VE of 60.3%. As observed in Study CYD14, the VE estimate in subjects aged 9 to 16 years was slightly higher and was of 65.6%.

In subjects aged 9 to 14 years included in Study CYD14, VE estimates by serotype were higher than in the overall population included in Study CYD14. Significant VE was observed for serotypes 1, 3 and 4. Lower efficacy was observed for serotype 2 and results were inconclusive as the lower bound of the 95% CI was below 0: VE was of 65.7% for serotype 1, 36.8% for serotype 2, 69.5% for serotype 3 and 87.9% for serotype 4. When pooling results from Study CYD14 and Study CYD15, significant efficacy was demonstrated for the 4 serotypes in subjects aged 9 to 16 years, with similar trends than in individual studies. VE was 58.4% for serotype 1, 47.1% for serotype 2, 73.6% for serotype 3 and 83.2% for serotype 4.

The variation of VE estimates by serotype was consistently observed in the several analyses conducted in each study, after at least 1 and 3 injections and in all subjects as well as in subjects aged 9 to 16 years. Whatever the analysis, moderate VE is shown for serotypes 1 and 2 and high VE is shown for serotypes 3 and 4.

7.4.3. VE against severe cases

VE against severe dengue cases (clinically severe as defined by the IDMC classification and DHF meeting any WHO criteria) due to any of the 4 serotypes are presented throughout the Active Phase (FASE population) for subjects aged 9 to 16 years and for all subjects included in the efficacy studies. Overall, dengue vaccine was highly effective in reducing the risk of severe dengue in subjects from 9 years of age. There was no evidence of increase of severity in dengue disease.

7.4.4. Incidence of hospitalised VCD cases

The incidence of hospitalised VCD cases due to any of the 4 serotypes is presented for cases reported throughout the Active Phase (FASE) in subjects aged 9 to 16 years and for all subjects included in the efficacy studies. A total of 101 subjects were hospitalised with VCD cases during the Active Phase. Overall, a reduction of approximately 67% of the incidence of hospitalised VCD cases due to any serotype in subjects receiving at least 1 injection was observed in the Dengue Group as compared to the Control Group. In subjects aged 9 years and above, the reduction in the incidence of hospitalised VCD cases due to any serotype was above 80%. In CYD15, a total of 60 subjects were hospitalised with VCD during the Active Phase. Overall, a reduction of 80% of the incidence of hospitalised VCD cases due to any serotype in subjects receiving at least 1 injection was observed in the Dengue Group as compared to the Control Group.

VE in preventing hospitalisation due to dengue was 72.7% throughout the Active Phase when pooling the 2 efficacy studies in all subjects, and above 80% when focusing on subjects aged 9 to 16 years. In both studies, the VE in preventing VCD cases leading to hospitalisation was also assessed by serotype. Limited data were obtained as few cases were reported, but the analysis showed that all four serotypes contribute to the overall reduction of incidence of hospitalised

VCD cases during the Active Phase. Overall there was a significant decrease in hospitalisation rates in subjects vaccinated with CYD dengue vaccine.

7.4.5. Covariate analysis

The potential impact of age (subjects aged 2 to 5, subjects aged 6 to 11 years and subjects aged 12 to 16 years) and of baseline dengue status on VE was assessed in Studies CYD14 and CYD15. The impact of baseline dengue status could only be assessed in the subset of subjects who were randomised to the immunogenicity analyses (2000 subjects in each study representing ~ 20% and ~ 10% of the populations of Studies CYD14 and CYD15, respectively). Additionally, the impact of age using a cut-off of 9 years of age was assessed in both studies to reflect the age for which the indication of the CYD dengue vaccine is sought.

7.4.5.1. VE by age groups

In the 2 large scale efficacy studies, significant VE was demonstrated in the different age groups. VE varied by age with older children and adolescents achieving the highest observed efficacy. In subjects aged 9 years and above, VE estimates in each individual study were above 64%. When pooling the 2 efficacy studies, VE estimate in subjects aged 9 years and over was 65.6% (95%CI: 60.7; 69.9. The same trend with increased VE estimates with age was observed against VCD due to each serotype, but this trend was less marked for serotype 2.

7.4.5.2. VE by baseline dengue immune status

VE by baseline dengue immune status is presented in each individual study in the randomised subset of 2000 subjects in each study who provided blood samples at baseline. Serotype 3 and 76.9% for serotype 4. In subjects aged 9 to 14 years included in Study CYD14, VE estimates by serotype were higher than in the overall population included in Study CYD14. Significant VE was observed for serotypes 1, 3 and 4. Lower efficacy was observed for serotype 2 and results were inconclusive as the lower bound of the 95% CI was below 0: VE was of 65.7% for serotype 1, 36.8% for serotype 2, 69.5% for serotype 3 and 87.9% for serotype 4. When pooling results from Studies CYD14 and CYD15, significant efficacy was demonstrated for the 4 serotypes in subjects aged 9 to 16 years, with similar trends than in individual studies. VE was 58.4% for serotype 1, 47.1% for serotype 2, 73.6% for serotype 3 and 83.2% for serotype 4.

The variation of VE estimates by serotype was consistently observed in the several analyses conducted in each study, after at least 1 and 3 injections and in all subjects as well as in subjects aged 9 to 16 years. Whatever the analysis, moderate VE is shown for serotypes 1 and 2 and high VE is shown for serotypes 3 and 4.

7.4.5.3. VE by country

In both efficacy studies, VE was assessed in each country. Varying levels of efficacy were observed in each country, reflecting the varying baseline dengue status of subjects included in the studies and the different circulation of serotypes in all countries included in the Phase III studies: in Study CYD14, VE estimates ranged from 51.1% in Vietnam to 79.0% in Malaysia, and in Study CYD15, VE ranged from 31.3% in Mexico to 77.7% in Brazil. Circulating dengue serotypes are important covariates of efficacy as shown by the varying VE estimates by country, which cannot be dissociated from varying levels of baseline seropositivity to dengue and circulation of the 4 serotypes. Indeed, lower efficacy was seen in countries with predominance of serotypes 1 and 2 during the study. Serotype prevalence and baseline status likely influence the observed efficacy by country.

7.4.6. Integrated immunogenicity analysis

The outcome measures used to describe the immune response to the CYD dengue vaccine, included GMTs, GMTR and seropositivity rates in each individual studies. Of the key immunogenicity parameters, GMT more highlights the age differences observed in immune responses. For the analyses by age group, data are described first in the claimed population, that

is, adults aged 18 to 60 years and subjects aged 9 to 17 years, and then in other age groups (adolescents aged 12 to 17 years, children aged 6 to 11 years and 2 to 5 years, and infants and toddlers aged below 2 years).

Levels of neutralising Ab were also assessed in subjects included in the Control Group. No significant increase in GMTs was observed in the control groups, regardless of age, baseline status and region.

7.4.7. Immunogenicity by age group in the claimed indication

Table 6 summarises the results from subjects in the claimed population, 9 through 60 years, included in studies conducted in endemic areas for adults and in the efficacy studies (Studies CYD23, CYD14 and CYD15) for subjects aged 9 to 17 years. GMT data is shown by age (subjects aged 9 to 17 years and adults 18 to 60 years) region and study at baseline and 28 days post-injection 3. Adult data is limited to the endemic AP region.

Table 6: Dengue immunogenicity summary in the claimed population pre-injection 1 and post-injection 3 - GMT of Ab against each serotype (1/dil) - Dengue PRNT

				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)
Adults (18 to 60* years)	Endemic AP	CYD22	20	327 (148; 725)	895 (335; 1443)	20	350 (168; 730)	825 (493; 1383)	20	160 (87.5; 291)	424 (286; 627)	20	75.0 (35.0; 161)	375 (251; 561)
		CYD28	148	15.8 (11.7; 21.5)	48.7 (33.6; 70.4)	148	16.9 (12.3; 23.1)	66.9 (47.9; 93.5)	148	14.3 (11.2; 18.7)	88.4 (68.6; 114)	148	10.1 (8.03; 12.7)	122 (96.5; 155)
		CYD47	126	184 (127; 268)	461 (340; 625)	126	204 (141; 294)	484 (370; 634)	126	219 (153; 312)	709 (552; 911)	126	55.4 (41.4; 74.2)	336 (271; 417)
9 to 17 years†	Endemic AP	CYD14	615	79.5 (65.9; 96.0)	255 (217; 299)	615	133 (111; 159)	530 (469; 600)	615	77.0 (64.6; 91.8)	289 (253; 331)	615	46.3 (39.8; 53.8)	201 (181; 223)
		CYD23	73	98.8 (54.9; 178)	276 (162; 471)	73	123 (69.4; 217)	490 (333; 721)	73	61.2 (37.5; 100)	457 (320; 651)	73	45.8 (29.1; 72.0)	197 (157; 249)
	Endemic LatAm	CYD15	1301	128 (112; 145)	395 (353; 441)	1301	138 (123; 156)	574 (528; 624)	1301	121 (108; 136)	508 (465; 555)	1301	43.6 (39.6; 48.0)	241 (226; 258)

* Subjects included in Studies CYD22, CYD28 and CYD47 were 18 to 45 years old; † Subjects included in Studies CYD23, CYD14 and CYD15 were 9 to 16 years old

Results show that Ab responses are higher in adults from endemic areas (Vietnam and India) than for areas of low endemicity (Singapore). Results in adults are also higher than in children and adolescents from the same endemic regions. In addition, GMTs in 9 to 17 year olds are similar or marginally higher in subjects from Latin America compared to AP regions depending on the specific serotype. In some studies, the humoral immune response to the CYD dengue vaccine was also assessed after the second injection. In the Phase III efficacy studies, overall post-injection 2 and post- injection 3 levels of neutralising Ab were similar. However, results between injections varied and depended on the specific serotype and the level of baseline Ab. Nevertheless, three injections provided assurance that the entire study population achieved the highest possible result.

7.4.8. Antibody persistence

Ab persistence data are available post-injection 3 up to 5 years in Study CYD05, up to 4 years in Studies CYD22 and CYD28, up to 1 year in Study CYD23, and up to 2 years in Studies CYD14 and CYD15. Based on the data currently available on long-term follow up, a predictable decrease in the level of circulating antibodies (GMTs) against all four serotypes is observed 2 years after the third injection in all studies, regardless of the age group (the same trend was observed in adults, adolescents and children). However, overall these GMTs remain several folds higher than the baseline values. From 2 to 4 years after the third injection, the data available show a trend to a stabilisation of the GMTs, which still remain overall above baseline against all 4 serotypes. The decrease observed between post-injection 3 and 2 year post-injection 3 varied according to age and dengue immune status at baseline.

7.4.9. Extrapolation of efficacy data in individuals 17 to 60 years

7.4.9.1. Extrapolation in individuals 17 to 45 years in endemic regions through immunological data

Although efficacy has not been evaluated in individuals above16 years of age, immunogenicity data from studies conducted in adults aged 18 to 45 years in Asia Pacific (Studies CYD22 and CYD47) suggest that adults have a high level of GMTs and respond well to the vaccine schedule used in the efficacy studies. Indeed, post-injection 3 Ab levels are generally higher than those seen in Studies CYD14 and CYD15 where efficacy was demonstrated.

7.5. Evaluator's conclusions on clinical efficacy

Efficacy was consistently demonstrated in the pivotal Phase III efficacy studies conducted over a 2-year period in two distinct geographic regions with circulation of the 4 serotypes in both. Overall, 55% to 65% VE was observed in preventing occurrence of VCD cases due to any serotype after at least one injection of the CYD dengue vaccine. Significant VE was also observed in preventing the occurrence VCD cases due to each serotype after at least one injection of the CYD dengue vaccine. This varied according to the serotype: moderate efficacy was observed for serotypes 1 and 2 and high efficacy was observed for serotypes 3 and 4.

A number of factors influence the overall VE of the CYD dengue vaccine. At the study level, the distribution of serotypes in the region or country influenced overall efficacy outcomes: when serotype 2 predominated, overall efficacy was lower. At an individual level, the subjects' age at vaccination, baseline immune status, and level of the response to the vaccine all had an effect on efficacy outcomes. Age also seems to influence the VE, with increasing VE in older subjects.

The primary endpoint of the two pivotal studies however was the prevention of confirmed dengue fever cases. This was shown in both studies in all age groups, in all countries and for all serotypes (although the vaccine is least effective for serotype 2). It was also more effective for older children. As a group, subjects aged 9 to 17 years showed a more favorable profile than the lower age groups. Subjects aged 2 to 5 years showed the lowest Ab responses to the vaccine and as a consequence, lower efficacy.

These pivotal studies had immunogenicity subsets which showed the development of antibodies, increasing levels with increasing age and prior exposure (baseline antibodies). The dengue immune status at baseline is an important factor influencing the response to the vaccine. Dengue immune subjects at baseline had higher post-injection Ab responses than age matched dengue non-immune subjects. Since subjects aged 2 to 5 years show a much higher proportion of dengue non-immune subjects at baseline, as expected, they had lower Ab responses and therefore lower efficacy. Subjects from endemic areas in the claimed population had the highest GMT while subjects in the 9 to 15 months old group had the lowest. Adults from endemic regions had overall higher GMTs than children and adolescents evaluated from the 2 pivotal efficacy studies.

These findings suggest that age is a key factor for predicting baseline status, reflecting increased accumulative exposure to dengue infection over time, subsequently influencing vaccine elicited immune response and thereby impacting efficacy outcomes.

7.5.1. Long-term efficacy

Currently, no data on the long-term efficacy of the vaccine is available in the intended population for use. Therefore, no conclusion can be drawn on long-term vaccine efficacy over time against all symptomatic VCD cases in the claimed population.

In order to further assess long-term efficacy, additional data on efficacy endpoints against all symptomatic VCD cases are now being captured in the long-term follow-up of the Phase III efficacy studies. In addition, booster will be evaluated in follow-up studies from Phase II studies

(Studies CYD63 and CYD64). For Study CYD63, a subset of subjects included in Study CYD28 (Phase II study conducted in Singapore) and who were 9 to 45 years at the time of inclusion will be asked to participate to Study CYD63 to receive a booster injection around 5 years after the last injection received in Study CYD28. For CYD64, a subset of subjects included in Study CYD13 (Phase II study conducted in Mexico, Honduras, Colombia and Puerto Rico) and in Study CYD30 (Phase II study conducted in Brazil) and who were 9 to 16 years at inclusion in these studies, will be asked to participate to Study CYD64 to receive a booster injection 4 to 5 years after the last injection received in Studies CYD13 or CYD30. These studies will assess the safety and immunogenicity of boosting.

8. Clinical safety

8.1. Criteria for analysis

Pre-defined solicited reactions (up to 14 days); local and systemic, and all unsolicited reactions (up to 28 days) were assessed in the reactogenicity subset (RS). They were collected for all individuals following each injection in all studies but Studies CYD23, CYD14 and CYD15, in which they were collected in a subset of subjects. All SAEs were collected up to at least 6 months after the last injection in studies assessing the final formulation of the CYD dengue vaccine given with the final schedule.

While all SAEs are collected in the Studies CYD14 and CYD15 efficacy studies out to 5 years post- injection 3, a limited set of SAEs (including related SAEs and hospitalised dengue cases) are collected in Studies CYD05, CYD22, CYD57 and CYD28 during the long-term follow-up of safety.

AESIs have been defined for the CYD dengue vaccine in all studies and are carefully monitored:

- Allergic reactions, including anaphylactic, as with any vaccine, within 7 days after injection.
- Acute viscerotropic or neurotropic disease (AVD, AND) within 30 days after injection: the risk of AVD and AND is linked to the surface antigens of the YF virus. As the CYD dengue vaccine has a YF backbone, AVD and AND are systematically followed as a preventive measure.
- Serious dengue diseases at any time during the study. Vaccine viremia was evaluated as an indicator of safety and is defined as the presence of vaccine viruses in the blood. Vaccine viremia was also assessed in subjects with acute febrile episodes within 28 days after vaccine injection, in dengue endemic regions (in Studies CYD08, CYD13, CYD22, CYD24, CYD28, CYD30, CYD33 and CYD23), to determine whether the fever was linked to the vaccine (positive vaccine viremia) or to dengue infection, in accordance with WHO guidelines. Dengue cases were also collected during the clinical development of the CYD dengue vaccine as an assessment of the safety of the vaccine and in accordance with WHO guidelines.

8.2. Severe dengue

Any of the serotypes can cause severe dengue and fatal disease. The occurrence of severe virologically confirmed dengue (SVCD) cases was assessed throughout the Active Phase of the Phase III efficacy studies and during the long-term safety follow-up.

8.3. Studies providing evaluable safety data

8.3.1. Pivotal studies that assessed safety as the sole primary outcome

Not applicable.

8.3.2. Pivotal and/or main efficacy studies

Both Studies CYD 14 and 15 provided safety data.

Overall, regardless of age, 21 clinical studies that used CYD dengue vaccine containing approximately 5 $\log_{10}$ CCID50 per serotype are included in the integrated safety analysis. A total of 16 studies administered CYD dengue vaccine in the final immunisation schedule of 3 injections administered 6 months apart and were considered the main studies for the integrated safety.

8.3.2.1. Other efficacy studies

5 studies administered CYD dengue vaccine in other immunisation schedule and were considered secondary studies providing supportive safety data.

8.3.2.2. Studies with evaluable safety data: dose finding and pharmacology.

Not applicable.

8.3.2.3. Studies evaluable for safety only

Not applicable.

8.4. Studies that assessed safety as the sole primary outcome

Not applicable.

8.5. Patient exposure

The safety database for the CYD dengue vaccine consists of all subjects who received at least one injection of the tetravalent CYD dengue vaccine containing ~5 log10 $CCID_{50}$ of each serotype administered with the final vaccination schedule, that is, 3 injections 6 months apart. Data were pooled and presented by age of study subjects: including adults (18 to 60 years), adolescents (12 to 17 years), children (2 to 11 years, further divided in 2 to 5 and 6 to 11 years), and infants and toddlers (below 2 years of age). To date, a total of approximately 28,900 subjects aged 9 months to 60 years have received at least one injection of the tetravalent CYD dengue vaccine, whatever the formulation, in completed or ongoing Phase I to Phase III clinical studies including the 2 ongoing efficacy Studies CYD14 and CYD15. A total of 28,653 received at least one injection of the final formulation, regardless of the schedule. Among these subjects, 21,215 subjects were in the claimed age indication (9 through 60 years of age). Approximately 20,600 subjects aged 9 to 60 years received at least one injection with the final schedule and approximately 19,700 subjects aged 9 to 60 years received 3 injections of CYD dengue vaccine with the final schedule. This database should allow for the detection of very common, common and uncommon AEs in accordance with WHO guidelines.

8.6. Adverse events

8.6.1. All adverse events (irrespective of relationship to study treatment)

8.6.1.1. Integrated safety analyses

A total of 4615 subjects aged 9 to 60 years (3068 were 9 to 17 years, and 1547 were adults aged 18 to 60 years) were included in the reactogenicity subset, in which solicited injection site and systemic reactions and unsolicited AEs were assessed. The pooled safety analysis, including

subjects 9 months to 60 years, describes the general safety profile of the vaccine. After each injection and any injection, the reactogenicity profile is comparable to the control vaccine when evaluated by age, gender, dengue immune status, endemic versus non endemic and region. In addition, the safety profile is similar across all populations studied as well as to placebo and currently licensed vaccines routinely given in similar age groups.

Unsolicited AEs

Slightly less than one half of subjects receiving dengue vaccine reported an unsolicited AE (from 44.2 to 46.2% of subjects). These were primarily medical conditions commonly seen for the age groups described and were mostly not severe and unrelated to vaccination. The incidence of unsolicited non-serious AEs tended to decrease with subsequent injections. Most unsolicited non- serious AEs were of Grade 1 and 2 intensity. Grade 3 AEs were reported by 5.4% of subjects aged 9 to 17 years and by 8.5% of adult subjects.

Unsolicited events reported for 28 days after vaccination were analysed across main studies, first by MedDRA System Organ Class (SOC), then by primary Preferred Term (PT). Slightly less than one half of subjects receiving dengue vaccine reported an unsolicited AE. In adults, 11.6% of subjects had at least one unsolicited AE related to injection by the study Investigators, whereas in subjects aged 9 to 17 years, 2.2% of subjects had at least one unsolicited AE assessed as related to injection. The most frequently reported non-serious unsolicited AEs were in the SOCs Infections and infestations, Respiratory, thoracic and mediastinal disorders, Gastrointestinal disorders, General disorders and administration site conditions, Nervous system disorders, in subjects aged 9 to 17 years and in adults, and Musculoskeletal and connective tissue disorders, injury, poisoning and procedural complications in adults only. Analysis of SOCs corresponding to reported reactions showed no clinically relevant differences between the CYD dengue vaccine and placebo. Each individual reaction was reported at a frequency below 3%. In adults and in subjects aged 9 to 17 years, non-serious unsolicited ARs were mostly Grade 1 or 2. Less than 1.5% of subjects (1.3% in adults and 0.2% in subjects aged 9 to 17 years) had an unsolicited AR of Grade 3 severity.

There were no safety concerns related to the nature and frequency of unsolicited AEs.

Similar trends were observed in adolescents (12 to 17 years), children (2 to 5 years and 6 to 11 years) and infants and toddlers (Dengue Groups only) as in subjects aged 9 to 17 years.

8.6.1.2. Main/pivotal studies that assessed safety as the sole primary outcome

N/A.

8.6.1.3. Pivotal and/or main efficacy studies

CYD 14

Unsolicited non-serious AEs

After the first injection, the percentage of subject experiencing at least one unsolicited AEs was similar in the 2 groups: 20.4% in the CYD Dengue Vaccine Group and 25.5% in the Control Group. For both groups, the most frequently reported unsolicited non-serious AEs were in the system organ class (SOC) Infections and infestations (11.9% in the CYD Dengue Vaccine Group and 15.7% in the Control Group), Respiratory, thoracic and mediastinal disorders (4.7% in the CYD Dengue Vaccine Group and 6.2% in the Control Group), and Gastrointestinal disorders (3.1% in the CYD Dengue Vaccine Group and 4.1% in the Control Group). These AEs were mainly reported as Grade 1, after 15 days after the first injection and lasted within 7 days. A total of 21 subjects reported at least one Grade 3 unsolicited non-serious AEs within 28 days (11 subjects (0.8%) in the CYD Dengue Vaccine Group and 10 subjects (1.5%) in the Control Group). The most common Grade 3 unsolicited non-serious AEs in the CYD Dengue Vaccine Group were in the SOC Infections and infestations.

After the second injection, there was a trend for less frequent unsolicited non-serious AEs (13.8% in the CYD Dengue Vaccine Group and 15.7% in the Control Group) as compared to the first injection (20.4% in the CYD Dengue Vaccine Group and 25.5% in the Control Group). There was similar frequency of reporting of unsolicited AEs after the second and after the third injection in both groups.

After any injection, 19 subjects (1.4%) in the CYD Dengue Vaccine Group and 6 subjects (0.9%) in the Control Group reported at least one unsolicited non-serious AE related to vaccination according to the Investigator (adverse reaction (AR)): the majority of the ARs were in the SOC General disorders and administration site conditions (11 subjects (0.8%) in the CYD Dengue Vaccine Group and 2 subjects (0.3%) in the Control Group), Skin and subcutaneous tissue disorders (3 subjects (0.2%) in the CYD Dengue Vaccine Group and 1 subject (0.2%) in the Control Group), and Infections and infestations (2 subjects (0.1%) in the CYD Dengue Vaccine Group and 1 subject (0.2%) in the Control Group). Related unsolicited AEs were mostly diseases or disorders commonly reported in subjects in this age range. Most were Grade 1 reactions. Only one Grade 3 unsolicited non-serious AR was reported: one subject reported a Grade 3 unsolicited non-serious AR (hypersensitivity) in the CYD Dengue Vaccine Group, after the first injection, that resolved within 2 days following health care contact and prescription of medication.

Study CYD 15

Immediate unsolicited AEs and reactions

A few immediate unsolicited AEs (0.2%) were reported within 30 minutes of vaccination in the 2 treatment groups that is, in 3 subjects in the CYD Dengue Vaccine Group and 1 subject in the Control Group. All occurred after Injection 1 and none led to subject's hospitalisation. Among these, only two (that is, Grade 3 asthmatic crisis and Grade 3 urticaria in one subject from the CYD Dengue Vaccine Group) were reported as related to vaccination by the investigators. They resolved respectively 2 and 3 days after onset and were considered as AESI.

Unsolicited non-serious AEs and ARs within 28 days of any injection

Unsolicited non-serious AEs were reported in 44.6% of subjects in the CYD Dengue Vaccine Group and 44.0% in the Control Group within 28 days after any injection. They were mostly common diseases or disorders of the childhood or adolescence, belonging to the following System Organ Classes (SOCs): 'Infections and infestations' (25.8% in the CYD Dengue Vaccine Group and 26.4% in the Control Group), 'Gastrointestinal disorders' (12.2% in the CYD Dengue Vaccine Group and 12.0% in the Control Group), 'Respiratory, thoracic and mediastinal disorders', (8.7% in the CYD Dengue Vaccine Group and 8.4% in the Control Group) or 'System nervous disorders', (7.9% in the CYD Dengue Vaccine Group and 6.8% in the Control Group). AEs from the other SOCs accounted for less than 5% in both groups.

Unsolicited non-serious AEs were mostly of Grade 1 or Grade 2 intensity. At least one Grade 3 unsolicited non- serious systemic AE was reported in 5.3% of subjects in the CYD Dengue Vaccine Group and in 3.9% of subjects in the Control Group. Most of these Grade 3 unsolicited non-serious AEs started after15 days or more post any injection and resolved within 7 days or less. The frequency of reported unsolicited non-serious AEs was stable in the 2 treatment groups over the doses. Few unsolicited non-serious AEs reported within 28 days after any injection were related to vaccination by the Investigator that is, in 1.2% of subjects in the CYD Dengue Vaccine Group and in 0.8% in the Control Group. Unsolicited non-serious ARs reported at the injection site were pain, haematoma, pruritus and anaesthesia in the CYD Dengue Vaccine Group and pain and induration in the Control Group. Unsolicited non-serious systemic ARs reported were malaise, abdominal pain, vomiting, dyspnoea, generalised erythema, vertigo, asthma crisis and urticaria in the CYD Dengue Vaccine Group and pruritus and lymphadenitis in the Control Group. Unsolicited non-serious ARs started within 3 days of any injection and mostly resolved within 3 days or less.

8.6.1.4. Other studies

Study CYD23

Unsolicited AEs

After the first injection, the percentage of subjects who experienced at least one unsolicited AE was similar in both groups (22.7% of subjects in the dengue group and 25.7% in the control group). These percentages were similar after the second injection (24.8% in the dengue group and 24.6% in the control group) and were slightly lower after the third injection (16.6% in the dengue group and 19.8% in the control group).

For both treatment groups, the most frequently reported unsolicited AEs were in the SOC 'infections and infestations' (across injections, the frequencies ranged from 10.2% to 16.1% in the dengue group and from 10.4% to 17.1% in the control group). After any injection, a maximum of 15 subjects (2.2%) in the dengue group and 14 of subjects (4.0%) in the control group reported Grade 3 unsolicited non-serious AEs. None of these AEs were considered as related to treatment.

8.6.2. Treatment related adverse events (adverse drug reactions)

8.6.2.1. Integrated safety analyses

Solicited injection site reactions were reported in approximately half of the subjects with a low proportion experiencing Grade 3 reactions in subjects aged 9 years and over, as shown in Table 7. In adult subjects, solicited injection site reactions were more frequently reported in the Dengue Group than in the placebo group, whereas similar trends were observed in the Placebo and Dengue Groups in subjects aged 9 to 17 years. The occurrence of solicited injection site reactions was similar in adults and subjects aged 9 to 17 years in the Dengue Group. Injection site pain was the most commonly reported reaction (more than 45% of subjects). The majority of these reactions was of Grade 1 intensity and resolved within 3 days without sequelae. Grade 3 reactions occurred at a rate below 1.5% in all age groups and were of short duration (< 3 days) and reversible. Rates of solicited injection site reactions remained similar after each successive injection. Similar trends were observed in children 2 to 11 years, in which reactogenicity tended to be more frequent than in adults in both the CYD dengue and placebo groups. In toddlers (Dengue Groups only), the occurrence of solicited injection site reactions tended to be lower compared to other age groups.

Table 7: Solicited injection site reactions after any CYD dengue vaccine injection during the solicited period – Subjects Aged 9 Years and Above – RS Main Studies Pooled

	Adults (18 to 60 years)			Subjects 9 to 17 years		
Subject with at least one	n/M	%	(95% CI)	n/M	%	(95% CI)
Solicited injection site reaction	714/1524	46.9	(44.3; 49.4)	1556/3050	51.0	(49.2; 52.8)
Grade 3 solicited injection site reaction	11/1524	0.7	(0.4; 1.3)	45/3050	1.5	(1.1; 2.0)
Pain	689/1524	45.2	(42.7; 47.7)	1502/3050	49.2	(47.5; 51.0)
Erythema	120/1524	7.9	(6.6; 9.3)	255/3049	8.4	(7.4; 9.4)
Swelling	37/1524	2.4	(1.7; 3.3)	209/3050	6.9	(6.0; 7.8)

Solicited systemic reactions after any CYD dengue vaccine injection are presented by age group in the claimed indication (9 through 60 years) in the reactogenicity subset in main safety studies. Overall, solicited systemic reactions tended to decrease after each successive injection. Headache was the most frequently reported reaction (approximately half of the subjects). The majority of these reactions was Grade 1 intensity, resolved within 3 days and was reversible. Grade 3 reactions occurred at rates around 10% in the claimed indication. Most Grade 3 solicited reactions were related to headache or fever. Fever occurred less frequently than

headaches (approximately 16% in subjects aged 9 to 17 years and less than 5% in adults) but tended to occur throughout the observation period for solicited reactions.

Table 8: Solicited systemic reactions after any CYD dengue vaccine injection during the solicited period - RS Main Studies Pooled

	Adults (18 to 60 years)			Subjects aged 9 to 17 years		
Subject with at least one	n/M	%	(95% CI)	n/M	%	(95% CI)
Solicited systemic reaction	999/1524	65.6	(63.1; 67.9)	2043/3050	67.0	(65.3; 68.7)
Grade 3 solicited systemic reaction	164/1524	10.8	(9.2; 12.4)	338/3050	11.1	(10.0; 12.2)
Fever	75/1522	4.9	(3.9; 6.1)	500/3040	16.4	(15.1; 17.8)
Headache	784/1524	51.4	(48.9; 54.0)	1649/3048	54.1	(52.3; 55.9)
Malaise	675/1524	44.3	(41.8; 46.8)	1247/3047	40.9	(39.2; 42.7)
Myalgia	643/1524	42.2	(39.7; 44.7)	1280/3047	42.0	(40.2; 43.8)
Asthenia	432/1524	28.3	(26.1; 30.7)	1042/3047	34.2	(32.5; 35.9)

In the Placebo Group, the incidence of each solicited systemic reaction was comparable to that of the Dengue Group for subjects aged 9 to 17 years, whereas incidence was slightly higher in the Dengue Group than in the Placebo group in adults. However, regardless of age, the time to onset and number of days of occurrence were similar in the Dengue Group and Placebo Group. Similar trends were observed in adolescents (12 to 17 years), in children (2 to 5 years and 6 to 11 years) and in toddlers (< 2 years of age) as in subjects aged 9 to 17 years.

For potential allergic reactions within 7 days, reactions of all seriousness and rash of all natures have been considered to calculate the frequency of these reactions:

- A total of 6 cases of rash have been reported in adults, (6/1547, uncommon); 2 cases have been reported in children aged from 9 years (rash and rash maculo-papular) (2/3068, rare);
- A total of 4 cases of urticaria have been reported in children aged from 9 years, including one related SAE (with a history of allergic rhinitis) (4/3068, Uncommon).

The reactions listed in the SPC are the following in subjects aged 9 to 60 years:

- Very common (≥ 10%): headache, myalgia, injection site pain, malaise, asthenia and fever;
- Common (≥ 1% and < 10%): Injection site reactions (erythema, hematoma, swelling, pruritus);
- Uncommon (≥ 0.1% and < 1%): lymphadenopathy, upper respiratory tract infection, dizziness, Migraine, oropharyngeal pain, cough, rhinorrhoea, nausea, rash, urticaria, neck pain, arthralgia, injection site induration, influenza-like illness. The most frequently reported adverse reactions (Very common and Common) are similar for children aged 9 to 17 years and for adults, with few differences in terms of frequency, that is, fever less frequently reported in adults (common) and injection site hematoma and pruritus less frequently reported in children aged 9 to 17 years (Uncommon).

Regarding the uncommon adverse reactions, age group specificities have been observed:

- Lymphadenopathy, migraine, arthralgia and influenza-like illness were reported only in adults;
- Urticaria was only reported in subjects aged 9 to 17 years;
- Upper respiratory tract infection, dizziness, oropharyngeal pain, cough, rhinorrhoea, nausea, rash and neck pain were less frequently reported in subjects aged 9 to 17 years (rare or very rare).

8.6.2.2. Pivotal and/or main efficacy studies

Study CYD14

Solicited injection site reactions

After the first injection, no difference was observed between the 2 groups in terms of solicited injection site reactions. In both groups, injection site pain was the most frequently reported solicited reaction (30.5% in the CYD Dengue Vaccine Group and 29.6% in the Control Group). Most of solicited injection site reactions were of Grade 1. Almost all solicited injection site reactions occurred within 3 days after injection and resolved within 1 to 3 days. Only one Grade 3 injection site reaction was reported: one subject in the CYD Dengue Vaccine Group experienced a pain recorded as Grade 3 for one day, after the first injection.

After the second injection, there was a trend of less injection site reactions reported (23.6% in the CYD Dengue Vaccine Group and 20.8% in the Control Group) compared with the first injection in both groups (32.4% in the CYD Dengue Vaccine Group and 31.5% in the Control Group). After the third injection, a similar incidence of injection site reactions was reported compared to after the second injection in both groups.

Solicited systemic reactions

After the first injection, no difference was observed between the 2 groups in terms of solicited systemic reactions. In both groups, headache and malaise were the most frequently reported solicited reaction (29.1% and 23.4%, respectively, in the CYD Dengue Vaccine Group and 25.3% and 22.3%, respectively, in the Control Group). Solicited systemic reactions were mostly reported as Grade 1. The majority occurred within 3 days after injection (except fever in the Control Group which occurred within 8 to 14 days) and resolved within 1 to 3 days.

Grade 3 solicited systemic reactions were reported in ≤ 1.4% of subjects and in similar frequency in both groups. Grade 3 fever was reported in 18 subjects (1.4%) and 7 subjects (1.1%), respectively, in the CYD Dengue Vaccine Group and the Control Group.

After the second injection, solicited systemic reactions tended to be less frequently reported (27.1% in the CYD Dengue Vaccine Group and 28.4% in the Control Group) compared with the first injection (40.4% in the CYD Dengue Vaccine Group and 37.3% in the Control Group). This was especially marked in the CYD Dengue Vaccine Group. There is similar frequency of reporting of solicited systemic reactions after the second and after the third injection in both groups.

Study CYD15

Overall, 74.8% of subjects in the CYD Dengue Vaccine Group and 75.1% in the Control Group experienced at least 1 solicited reaction after any injection.

Solicited local reactions

Injection site reactions within 7 days of any injections were reported in 50.8% of subjects in the CYD Dengue Vaccine Group and 42.4% in the Control Group and Grade 3 injection site reactions were reported in 2.0% of subjects in the CYD Dengue Vaccine Group and 1.4% in the Control Group. Pain was the injection site reaction most frequently reported after any injection in the 2 groups (48.9% in the CYD Dengue Vaccine Group and 41.0% in the Control Group). Erythema and swelling were less frequently reported (less than 10% in the 2 groups). Injection site reactions tended to decrease after the second injections and remained stable after the third injection in both groups. Most injection site reactions started within 3 days of each injection and were present for 3 days or less during the solicited period. The proportion of Grade 3 injection site reactions did not increase with the number of injections.

Solicited systemic reactions

Systemic reactions within 14 days of any injection were reported in 68.4% of subjects in the CYD Dengue Vaccine Group and 69.5% in the Control Group and Grade 3 systemic reactions were reported in 13.9% of subjects in the CYD Dengue Vaccine Group and 11.4% of subjects in the Control Group. Headache was the systemic reaction the most frequently reported after any injection in the 2 groups (54.7% in the CYD Dengue Vaccine Group and 57.5% in the Control Group). Malaise, myalgia and asthenia were also commonly reported (between 37.3% and 43.4% in the 2 groups) and fever was the least reported (16.7% in the CYD Dengue Vaccine Group and 18.8 % in the Control Group). All systemic reactions except fever tended to decrease after the second injection and remained stable after the third one. The proportion of fever remained stable after each injection in the 2 treatment groups. Most systemic reactions started within 3 days of each injection, except for fever that could start any time within 14 days of any injection. Most of these reactions were present for 3 days or less during the solicited period.

8.6.2.3. Other studies

Study CYD23

Solicited injection site reactions

After the first injection, the frequency of each injection site reaction was similar between treatment groups. In both treatment groups, pain was the most frequently reported injection site reaction (33.5% in the dengue group and 30.9% in the control group), followed, to a lesser extent, by erythema (13.3% in the dengue group and 16.3% in the control group) and swelling (9.0% in the dengue group and 9.2% in the control group). After the second and third injections, the percentages of subjects with pain, erythema or swelling were similar to those observed after the first injection. Grade 3 solicited reactions were infrequent in both treatment groups (4.8% in the dengue group and 7.7% in the control group) and were mostly reported after the first injection. In both treatment groups, almost all injection site reactions occurred within 3 days after injection and resolved within 1 to 3 days.

Solicited systemic reactions

The proportion of subjects with solicited systemic reactions after the first injection was similar in both treatment groups, with the exception of myalgia that tended to be more frequent in the dengue group. Headache was the most frequently reported solicited systemic reaction (39.6% in the dengue group and 35.2% in the control group). Malaise, myalgia and asthenia were reported to a lesser extent (approximately 25-30%, each) and fever was the least reported (13.8% in the dengue group and 14.7% in the control group). After the second and third injections, the percentages of subjects with headache, myalgia, malaise, or asthenia were similar to those observed after the first injection. Grade 3 systemic reactions were infrequent in both treatment groups (4.6% in the dengue group and 7.4% in the control group) and were mostly reported after the first injection. In both treatment groups, almost all solicited systemic reactions occurred within 3 days after injection and resolved within 1 to 3 days.

8.6.3. Deaths and other serious adverse events

8.6.3.1. Integrated safety analyses

The frequency and nature of SAEs were similar between the CYD dengue vaccine and control groups, and mostly corresponded to common medical conditions expected in each age group. Within 28 days after any injection, 0.6% of adolescents to 1.0% of adult subjects reported at least one SAE. From 28 days to 6 months after any injection, the proportions of subjects with at least one SAE ranged from 2.4% in adolescents to 3.6% in toddlers. These events were isolated in nature and frequency, and mainly belonged to the system organ class 'Infections and Infestations'. No cluster of clinical patterns of SAEs up to 28 days post-injection was observed. Few neurological SAEs were reported after CYD dengue vaccine (occurrence at a maximum of 0.3% in adult subjects) and they were isolated in nature and frequency. There were few related

SAEs observed up to 28 days after any injection: 2 in adults (headache and polymyalgia rheumatic) and 4 in subjects aged 9 to 17 years (urticaria, asthma, acute polyneuropathy and tension headache). A single SAE (blighted ovum) was assessed as related to the CYD dengue vaccine by the Investigator between 28 days and 6 months after any injection. Additionally, 1 SAE of convulsion in an 11-year-old subject was assessed as related to the study vaccine. In the placebo group, 2 related SAEs were observed (pyrexia and visual impairment) within 28 days after any injection, both in subjects aged 9 to 17 years.

8.6.3.2. Pivotal and/or main efficacy studies

Study CYD14 SAEs active phase

One immediate SAE was reported as related to the study procedure by the Investigator in the CYD Dengue Vaccine Group, a suspect hypoglycaemic malaise 6 minutes after the first injection. Within 28 days after any injections, 87 subjects reported a total of 88 SAEs (0.8% in the CYD Dengue Vaccine Group and 1% in the Control Group respectively). Most SAEs were in the SOCs Infections and Infestations (26 subjects (0.4%) in the CYD Dengue Vaccine Group and 18 subjects (0.5%) in the Control Group), Injury, poisoning and procedural complications (11 subjects (0.2%) in the CYD Dengue Vaccine Group and 6 subjects (0.2%) in the Control Group), and Nervous system disorders (6 subjects (< 0.1%) in the CYD Dengue Vaccine Group and 5 subjects (0.1%) in the Control Group). Overall, there was no cluster of events within 28 days post any injection in term of nature or time to onset from injection.

A total of 575 subjects experienced 647 SAEs during the Active Phase of the trial. There were no differences between treatment groups: 355 subjects (5.2%) in the CYD Dengue Vaccine Group and 220 subjects (6.4%) in the Control Group. During the 6 month follow-up period, most SAEs were in the SOCs Infections and Infestations (161 subjects (2.4%) in the CYD Dengue Vaccine Group and 110 subjects (3.2%) in the Control Group), Injury, poisoning and procedural complications (58 subjects (0.8%) in the CYD Dengue Vaccine Group and 19 subjects (0.6%) in the Control Group) and Gastrointestinal disorders (26 subjects (0.4%) in the CYD Dengue Vaccine Group and 8 subjects (0.2%) in the Control Group).

Among the 647 SAEs reported, a total of 2 SAEs (< 0.1%) was assessed as related to treatment by the Investigator:

- Acute disseminated encephalomyelitis reported in an 8-year-old male child in the CYD Dengue Vaccine Group 7 days after the first injection. The subject, without detectable vaccine virus in blood or cerebrospinal fluid, recovered 15 days later without clinical sequelae and there was no recurrence of event. The subject was not withdrawn from the study and was still followed-up for safety purpose but no additional injections were given
- Allergic angioedema with swelling of face and generalised urticaria 18 days after the first injection reported in a subject in the Control Group.

Few neurological unrelated SAEs were reported within 28 days (6 subjects (< 0.1%) in the CYD Dengue Vaccine Group and 5 (0.1%) in the Control Group) and during the 6 month follow-up (20 subjects (0.3%) in the CYD Dengue Vaccine Group and 11 subjects (0.3%) in the Control Group).

No immediate hypersensitivity or allergic reactions, and no cases of viscerotropic or neurotropic disease, were reported.

Study CYD14 SAEs hospital phase

During the first year of Hospital Phase, 163 subjects (2.4%) and 89 subjects (2.6%) experienced at least one SAE in the CYD Dengue Vaccine Group and in the Control Group, respectively. This corresponds to 174 and 94 SAEs reported in the CYD Dengue Vaccine Group and in the Control Group, respectively. These events were all reported as unrelated to vaccination.

Study CYD14 active phase; deaths

Four deaths were reported in the CYD Dengue Vaccine Group, all of them were not related to vaccination (3 traffic accidents and one tracheal injury). One death was reported in the Control Group (subject diagnosed with acute lymphoblastic leukemia during the Active Phase, died during the first year of the Hospital Phase).

Study CYD14 hospital phase; deaths

One death was reported during the Hospital Phase in the Control Group (subject diagnosed with encephalitis during the first year of Hospital Phase).

Study CYD15 active phase SAEs

A total of 875 subjects reported at least 1 SAE during the Active Phase: 567 (4.1%) in the CYD Dengue Vaccine Group and 308 (4.4%) in the Control Group. Most SAEs reported during the Active Phase were diseases or injuries commonly reported in the childhood and adolescence which belonged to the SOCs: 'Infections and Infestations' (293 subjects (2.1%) in the CYD Dengue Vaccine Group and 188 subjects (2.7%) in the Control Group), 'Injury, poisoning and procedural complications' (103 subjects (0.7%) in the CYD Dengue Vaccine Group and 35 subjects (0.5%) in the Control Group). SAEs from the other SOCs accounted for less than 0.5% in both groups.

A total of 122 subjects: 82 (0.6%) in the CYD Dengue Vaccine Group and 40 (0.6%) in the Control Group, reported a total of 127 SAEs within 28 days of any injection: 85 in the CYD Dengue Vaccine Group and 42 in the Control Group. In both groups, most SAEs reported within 28 days after any injection were diseases or injuries commonly reported in the childhood and adolescence which belonged to the following SOCs: 'Infections and Infestations' (37 subjects (0.3%) in the CYD Dengue Vaccine Group and 16 subjects (0.2%) in the Control Group), 'Injury, poisoning and procedural complications' (15 subjects (0.1%) in the CYD Dengue Vaccine Group and 4 subjects (< 0.1%) in the Control Group), as well as 'Gastrointestinal disorders' (for example, abdominal pain, inguinal hernia) and 'Nervous system disorders' (for example, convulsion, epilepsy) , 'Respiratory, thoracic and mediastinal disorders' (for example, asthma) and 'Skin and subcutaneous tissue disorders' (for example, urticaria) reported in < 0.1% of subjects in each SOC, in the two groups. No pattern (cluster) of events was found within 28 days after vaccination.

A total of 4 SAEs (< 0.1%) were assessed as related to the vaccine by the Investigator and the sponsor during the Active Phase: 3 in the CYD Dengue Vaccine Group and 1 in the Control Group.

In the CYD Dengue Vaccine group, acute polyneuropathy, asthma and allergic urticarial were reported. These SAEs occurred between few hours to 3 days post Injection 1 or Injection 2. Of these 3 SAEs, only acute polyneuropathy required hospitalisation. One additional SAE was assessed as related to vaccination by the sponsor but not the Investigator. Unspecified seizures were reported 18 hours after Injection. This case required hospitalisation and resolved the same day. In the Control group, visual impairment was reported 21 hours post-injection 1. Subject was hospitalised and recovered 3 days after SAE onset.

During the period from D0 to the end of the 6 months follow-up, 641 subjects, 411 (3.0%) in the CYD Dengue Vaccine Group and 230 (3.3%) in the Control Group, reported a total of 706 SAEs (450 in the CYD Dengue Vaccine Group and 256 in the Control Group respectively). Similar results were observed in the Control Group. Among the 704 SAEs reported from D0 up to 6 months after the third injection, no other SAEs than the 4 reported within 28 days after the first and the second injections were assessed as related to treatment.

During the period from the 6 months follow-up up to the end of the first year of the Hospital Phase, 701 subjects, 454 (3.3%) in the CYD Dengue Vaccine Group and 247 (3.6%) in the Control Group, reported a total of 768 SAEs (506 in the CYD Dengue Vaccine Group and 262 in

the Control Group, respectively). Among the 1474 SAEs reported from D0 up to 24 months after the third injection, no other SAEs than the 4 reported within 28 days after the first and the second injections were assessed as related to treatment by the Investigator.

Study CYD15 active phase deaths

There were 12 deaths reported during the Active Phase, 6 in each treatment group. Most deaths were accidental or the consequence of injuries. None of deaths was assessed as related to product by the Investigator or the sponsor.

Study CYD15 hospital phase deaths

There were 5 deaths reported during the first year of the Hospital Phase, 4 in the CYD Dengue Vaccine Group and 1 in the Control Group. None of deaths was assessed as related to product by the Investigator or the sponsor.

Serious associated viscerotropic disease (AVD) and serious associated neurotropic disease (AND) No event of viscerotropic or neurotropic disease was observed.

Study CYD15 serious dengue disease

During the Active Phase, serious dengue disease events were reported in 41 subjects in the CYD Dengue Vaccine Group and 48 subjects in the Control Group; 14 out of 41 (34.1%) in the CYD Dengue Vaccine Group and 40 out of 48 (83.3%) in the Control Group were virologically confirmed.

During the first year of the Hospital Phase, serious dengue disease was reported in 22 subjects (0.2%) in the CYD Dengue Vaccine Group and 18 subjects (0.3%) in the Control Group.

8.6.3.3. Other studies

Study CYD23

A total of 586 SAEs were reported during the study (584 occurred during the Active Phase).The percentages of subjects reporting SAEs during the Active Phase were similar between treatment groups; 11.8% of subjects in the dengue group and 13.2% of subjects in the control group reported SAEs.

Among the 586 SAEs reported, only 1 SAE (in the control group) was assessed as related to treatment by the Investigator: a female subject with a diagnosis of acute febrile illness. Five deaths were reported, 4 occurred in the control group and 1 in the dengue group. None of them was considered as related to treatment.

8.7. Evaluation of issues with possible regulatory impact

No safety concerns were raised from the analysis of the biological safety parameters. The majority of subjects had biological values within normal ranges both at baseline and after any CYD dengue vaccine injection and at any day. The most frequent abnormalities after any CYD dengue vaccine injection and any day were decreased hematocrit and decreased hemoglobin, decreased and increased WBC count, and increased AST.

Biological safety abnormalities classified as Grade 3 were reported by low percentages of subjects (2.2% or less, depending on the parameter), and the most frequent ones were decreased haemoglobin and neutropenia.

8.7.1. Liver function and liver toxicity

N/A.

8.7.2. Renal function and renal toxicity

N/A.

8.7.3. Other clinical chemistry

N/A.

8.7.4. Haematology and haematological toxicity

N/A.

8.7.5. Other laboratory tests

N/A.

8.7.6. Electrocardiograph findings and cardiovascular safety

N/A.

8.7.7. Vital signs and clinical examination findings

N/A.

8.7.8. Immunogenicity and immunological events

8.7.8.1. Study CYD14 AESIs

No immediate anaphylactic shock has been reported. The proportions of subjects who experienced at least 1 non-serious potential allergic reaction within 7 days after any injection was low, ranging from 0.5% in adolescents to 1.2 % in adults, and comparable in the Dengue Group and in the Placebo Group. The proportions of subjects in the claimed indication who experienced at least 1 non-serious potential allergic reaction within 7 days after any injection was 1.2% in the Dengue Group and 0.3% in the Placebo Group in adults and 0.5% in both groups in subjects aged 9 to 17 years. Less than 0.1% of subjects experienced at least 1 serious potential allergic reaction in the Dengue Group in subjects aged 9 to 17 years and adults. Only 5 subjects experienced a serious potential allergic reaction in the Dengue Group (1 adult and 4 subjects aged 9 to 17 years): 4 subjects experienced asthma or asthmatic crisis and had a relevant medical history of asthma, asthmatic bronchitis, or bronchial obstructive symptoms; 1 subject experienced urticaria and had a history of allergic rhinitis. Two of these serious potential allergic reactions (urticaria and asthma) were assessed as related to the study vaccine.

No confirmed viscerotropic and neurotropic events were reported in any study. There was no excess of clinically severe VCD cases in vaccine recipients compared to controls in the observation period, mainly 25 month of follow-up after first dose.

Non-serious hypersensitivity/allergic reactions within 7 days after any injection

Seven subjects experienced at least one non-serious hypersensitivity/allergic reaction AESI within 7 days of any injection that is, 4 in the CYD Dengue Vaccine Group (2 subjects experienced dyspnoea, 1 subject developed generalised erythema, and 1subject experienced asthmatic crisis and urticaria) and 3 in the Control Group (asthma (2 episodes), and pruritus). Most were of Grade 1 intensity except asthmatic crisis and urticaria that were of Grade 3. They did not lead to discontinuation from further injections except asthmatic crisis and urticaria. In addition to asthmatic crisis and urticaria, one of the 2 episodes of dyspnoea, generalised erythema in the CYD Dengue Vaccine Group, and pruritus in the Control Group were assessed as related to study product.

Serious hypersensitivity/allergic reactions within 7 days after any injection

Five subjects experienced at least one serious AESI hypersensitivity/allergic reaction within 7 days of any injection: 4 in the CYD Dengue Vaccine Group (2 subjects had asthma, 1 subject had asthmatic crisis and 1 subject developed urticaria) and 1 in the Control Group (asthma). In the CYD Dengue Vaccine Group, one case of asthma and the case of urticaria occurred within 24 hours of the vaccine injection (post-Injection 1 and post-Injection 2, respectively). These 2 SAEs did not require hospitalisation but subjects were discontinued from the following injections.

Both SAEs were assessed as related to vaccination by both the Investigator and the sponsor. All serious AESIs resolved.

8.7.9. Serious skin reactions

Discussed above.

8.7.10. Other safety parameters

8.7.10.1. Integrated safety analyses

No evidence of increased risk of SVCD was observed in the Dengue Group compared to the Control Group during the 25 month observation period of active surveillance in each of the 3 efficacy studies overall or in the pooled analysis: 27 SVCD cases were reported in subjects 9 to 16 years who received at least 1 injection in the efficacy studies (4 in the Dengue Group and 23 in the Control Group) with a RR of 0.087 (95% CI: 0.02; 0.25) showing a statistically significant reduction of SVCD cases in the Dengue Group compared to the Control Group in this population during the Active Phase. Additionally, there was no evidence of increase in severity of SVCD cases based on the review of clinical outcomes and hospitalisation rates.

Long-term safety follow-up

Long-term follow-up was defined as the period from Month 6 after the last injection onward for SAEs and from Year 1 after the last injection onward for dengue cases.

At the time of submission, the following data from on-going long-term follow-up are available from the efficacy studies:

- Study CYD57: full data from the first 2 years of Hospital Phase (Hospital Phase Year 1 and Year 2, that is, 2 and 3 years after the end of the Active Phase in CYD23) and preliminary data from the third a and fourth years of Hospital Phase (cut-off date on 13 August 2015).
- Studies CYD14 and CYD15: full data from the first year of Hospital Phase (Hospital Phase Year 1, that is, 2 years after the end of the Active Phase in CYD14 or CYD15 and 3 years after the last injection) and preliminary data from the second and third years of follow-up (Hospital Phase Year 2 and Year 3) (cut-off date on 13 August 2015).

8.7.10.2. SAEs

No safety concerns were identified during long-term follow-up of all studies having a long-term follow-up (Cut-off date on 01 September 2015), as no evidence of excess of any specific SAEs were reported. In particular, no related SAEs were reported in the Dengue Group.

8.7.10.3. Hospitalised VCD cases during completed years

The incidence of hospitalised VCD cases during the long-term follow-up of the efficacy studies (Studies CYD14, CYD15 and CYD57) was assessed by age group in each individual study, that is, in subjects aged 2 to 5 years, 6 to 11 years and 12 to 14 years, as applicable.

The analyses from the Hospital Phase in Study CYD14 showed a higher incidence of hospitalised VCD cases in the Dengue Group compared to the Control Group in subjects aged 2 to 5 years at enrolment. The annual incidence rate of hospitalised VCD cases was 1.0% in the dengue group and 0.1% in the placebo group representing a relative risk (RR) of 7.454 (95% CI: 1.15; 313.80). In subjects aged 6 years and above at enrolment, the RR of hospitalised VCD cases was below 1 during the first year of the Hospital Phase, and this RR decreased with increasing age (RR < 1: 0.627 (95% CI: 0.22; 1.83) in subjects aged 6 to 11 years and RR < 1: 0.249 (95% CI: 0.02; 1.74) in subjects aged 12 to 14 years).

In the long-term follow-up of the Phase IIb efficacy study (Study CYD57, with subjects aged 4 to 11 years at inclusion in Study CYD23); RR of hospitalised VCD cases varied each year and according to serotypes distribution and age groups. As for Study CYD14, the RR fluctuated over time in young age groups (4 to 5 year-old subjects), with RR of 2.443 and 0.814 the first and

second years of hospital phase, respectively, while RR remained consistently below < 1 in older age groups (6 to 11 year-old subjects).

Conversely for Study CYD15, the analyses from the first year of Hospital Phase did not show any difference of incidence of hospitalised VCD cases between the Study CYD dengue and control groups. The annual incidence rate of hospitalised VCD cases in 9 to 11 year-old subjects was 0.2% in the dengue group and 0.3% in the placebo group representing a relative risk (RR) of 0.554 (95% CI: 0.20; 1.54). Similarly, the annual incidence rate of hospitalised VCD cases in 12 to 16 year-old subjects was < 0.1% in the dengue group and 0.2% in the placebo group representing a relative risk (RR) of 0.501 (95% CI: 0.13; 1.87).

To further inform the benefit/risk ratio of the CYD dengue vaccine, breakdown analyses were performed at different age cut-offs. The cut-off below and above 9 years of age was chosen defining different age groups: (i) subjects aged between 2 and 8 years and (ii) subjects aged between 9 and 14 years). The results in Studies CYD14 and CYD57 were compared to that observed in subjects from 9 years of age included in Study CYD15 where RR was consistently < 1 during the first year of Hospital Phase.

The incidence of hospitalised VCD cases during the first 2 years of the Hospital Phase in Study CYD57 and during the first year of the Hospital Phase in Studies CYD14 and CYD15 is presented with the cut-off at 9 years of age. In both Studies CYD14 and CYD57, the analysis shows a lower RR in subjects aged 9 to 14 years compared to children aged 2 to 8 years. The RR in subjects aged 9 to 14 years in Study CYD14 (0.572) was similar to RR in subjects aged 9 to 16 years measured in Study CYD15 (0.533).

When comparing RR against hospitalised VCD cases in subjects aged 9 to 14 years during the Active Phase in Studies CYD14 and CYD15 (0.185 and 0.197, respectively), to the RR during the first year of Hospital Phase (0.572 and 0.533, respectively), there appears to be a trend toward a higher risk of hospitalised VCD cases in this age group. However, when considering the cumulative data collected during the Active Phase and the first year of Hospital Phase in subjects aged 9 to 14 years included in Studies CYD14 and CYD15, the RR during the entire study remained significantly < 1 with a value of 0.273 (95% CI: 0.14; 0.50) and 0.284 (95% CI: 0.18; 0.44), respectively. These results are in favour of a decreased risk of hospitalised VCD cases in the Dengue Group throughout the studies. The same trend was observed in CYD57, with RR in subjects aged 9 to 11 years significantly < 1 during the entire study (0.290 (95% CI: 0.13; 0.62)).

8.7.10.4. Clinical signs and symptoms of hospitalised VCD cases: hospital versus active phase

Hospitalised VCD cases observed during the first year of Hospital Phase in the Dengue Group did not show a different clinical profile in terms of severity compared to the Control Group in the Hospital Phase and also compared to the Active Phase. The mean duration of fever, clinical symptoms, and hospitalisation was similar in the 2 treatment.

8.7.10.5. Viremia Levels in hospitalised VCD cases: hospital versus active phase

Case viremia levels were similar during the Active and the Hospital Phases. No increase of viremia was observed in CYD dengue vaccine recipients compared to placebo recipients. In vitro and clinical data available so far indicates that CYD vaccination does not increase post-dengue disease viremia and thus, dengue severity.

8.7.10.6. Hospitalised VCD cases during uncompleted years (preliminary data)

Study CYD57 Year 3 and Year 4 Hospital Phase, Studies CYD14 and CYD15 Year 2 and Year 3 Hospital Phase are incomplete years (data collection is still ongoing or data are still unlocked). Therefore, data from these incomplete years are preliminary data obtained from non-validated databases and not analysed as per pre-planned interim analysis.

Preliminary data showing the number of hospitalised VCD cases collected up to the 13 August2015 during the ongoing follow-up of Studies CYD14, CYD15 and CYD57 show to date:

- In Studies CYD14 and CYD15, there were less VCD cases reported in the Dengue Group than in the Control Group.
- In Study CYD57 during ongoing Year 4 Hospital Phase, there were 7 cases reported and all were in the Dengue group. In Studies CYD14 and CYD57, there were more VCD cases reported in the Dengue Group compared to the Control group in subjects < 9 years of age.
- Severe VCD Cases during Completed Years in Study CYD14, among the 40 hospitalised VCD cases reported during the first year of the Hospital Phase, 12 were assessed as clinically severe: 11 in the Dengue Group and 1 in the Control Group. As observed with hospitalised VCD cases, when considering the age group at enrolment, during the first year of the Hospital Phase, there was an unexplained difference of hospitalised SVCD cases between the Dengue Group and the Control Group in children aged 2 to 5 years (6 cases) and 6 to 11 years (5 cases). However RR was not calculated because there was no case in the Control Group. This difference between treatment groups was not seen in adolescents aged 12 to 14.
- In subjects aged 9 to 14 years, the RR against hospitalised SVCD cases during the first year of the Hospital Phase in Study CYD14 was 1.5 with a large CI which did not allow drawing definitive conclusions. However, during the entire study, the RR against hospitalised SVCD cases was < 1 and statistically significant (95% CI: 0.06; 0.71), indicating a decreased risk of SVCD cases in the Dengue Group compared to the Control Group. In CYD15, the RR against hospitalised SVCD cases during the first year of the Hospital Phase was 0.300 (95% CI: 0.05; 1.54). Similarly to Study CYD14, the RR against hospitalised SVCD cases during the entire study was < 1 and statistically significant (95% CI 0.02; 0.33), indicating a decreased risk of SVCD cases in the Dengue Group compared to the Control Group.

8.8. Other safety issues

8.8.1. Safety in special populations

The vaccine was not studied in pregnancy but there were a total of 404 pregnancies reported in the CYD dengue vaccine studies: 341 were unexposed, 36 were exposed but not yet pregnant, 22 were exposed and pregnant and exposure could not be determined for 5 pregnancies. Among 22 female subjects who were exposed to CYD dengue vaccine during their pregnancy, 3 had adverse pregnancy outcome (death in utero, stillbirth and blighted ovum). In all cases important risk factors were identified. There was no difference between the 2 groups when compared to placebo in adverse pregnancy outcomes. In conclusion, no safety concerns were raised from the review of these adverse pregnancy outcomes.

8.9. Post marketing experience

There is none available yet as the first regulatory authorities (Mexico, the Philippines and Brazil) only granted marketing authorisation to the CYD dengue vaccine in December 2015.

8.10. Evaluator's overall conclusions on clinical safety

The safety profile of the CYD dengue vaccine was acceptable within 6 months post any injection in all the populations studied, that is, in all age groups and regions (non-endemic, endemic AP, or endemic Latin America), and irrespective of gender and dengue, FV, JE or YF status at baseline. Approximately 28,900 subjects aged 9 months through 60 years were randomised in 22 trials, to receive at least one injection of the tetravalent CYD dengue vaccine, regardless of the formulation and schedule. The database including the 22 studies in the pooled/integrated

analysis should allow for the detection of very common, common, and uncommon AEs and SAEs with an incidence ≥ 0.1% with a probability of at least 95%. This level of precision was in accordance with WHO guidelines.

The safety 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 Dengue Group than in the Placebo Group. The safety profile of the CYD dengue vaccine (reactogenicity) was also found to be similar to that of comparator vaccines, that is, different licensed vaccines mainly used as benefit vaccines or as part of the vaccination schedules of the age groups.

Solicited reactions were reported in a majority of subjects, regardless of age. Most of the solicited reactions within 7 days (injections site reactions) or 14 days (systemic reactions) were Grade 1 and resolved spontaneously within 1 to 3 days of onset. Immediate systemic AEs within 30 minutes after any injection as well as AEs leading to discontinuation occurred in 1.6% in adults or less (0.2% to 0.6%) in the younger subjects.

The incidence of unsolicited non-serious ARs was low in adolescents, children and toddlers (0.4% to 2.5%) but more frequently reported in adults (approximately 12%). No clusters of ARs were observed in any of the age groups. Grade 3 unsolicited non-serious ARs were reported by low proportions of subjects (1.3% or less) depending on the age group. Most unsolicited non-serious AEs and ARs were of Grade 1 and resolved spontaneously.

The incidence of solicited systemic reactions and unsolicited non-serious AEs and ARs tended to decrease with subsequent injections, while the incidence of solicited injection site reactions was similar after each injection. 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 diseases, infections or injuries commonly reported in these age groups, and no cluster in terms of nature and frequency was observed.

In the Dengue Group, SAEs assessed as related to the study vaccine occurred in 7 subjects within 28 days of injections, 2 adults (headache and polymyalgia rheumatica), 1 adolescent (urticaria), and 4 children (ADEM, asthma, acute polyneuropathy, tension headache). None was reported in infants and toddlers. One SAE (blighted ovum) in an adult, assessed as related to the study vaccine, occurred between 28 days and 6 months after the injection. One SAE (convulsion) in a child was assessed as related to the study vaccine by the sponsor.

A total of 4 Neurological disorder SAEs within 30 days were assessed as related to the study vaccine by the Investigator (headache, tension headache, acute polyneuropathy, and ADEM) in addition to convulsion that was assessed as related to the study vaccine by the sponsor. They were isolated events and for ADEM, acute polyneuropathy and convulsion, no vaccine viruses were isolated from the subjects. During the long-term safety follow-up, no SAEs assessed as related to the study vaccine were reported from Month 6 onwards after the last injection in the Dengue Group. No deaths were linked to dengue cases.

Less than 6% (38 subjects out of 683) subjects had vaccine viremia after administration of the CYD dengue vaccine. In each case, vaccine viremia recorded was low, that is, very close to the LLOQ value, and no safety concerns were observed in these subjects.

The analysis of AESIs showed no particular concerns in terms of allergic reactions. In addition, very few potential allergic reactions were rated as Grade 3 or serious. No events of viscerotropic or neurotropic disease were observed after administration of the CYD dengue vaccine was observed in any studies. Serious dengue disease events did not raise any safety concern.

Three abnormal pregnancy outcomes were observed in 22 women who were exposed to the CYD dengue vaccine during their pregnancy (death in utero, stillbirth and blighted ovum). In all cases risk factors were identified. Furthermore, no difference in abnormal pregnancy outcomes

was observed between the Dengue Group and the Placebo Group. No data on lactation were collected.

During the Active Phase, no increase of risk of SVCD disease was observed. There was no excess of SVCD due to any serotype in subjects in the Dengue Group compared to the Control Group regardless of the age of the population in the 3 efficacy trials CYD14, CYD15, and CYD23. In both adolescents and children, SVCD occurred with a low and similar density incidence in the endemic AP and endemic Latin America regions, and there was no excess of SVCD in the Dengue Group compared to the Control Group in the 2 endemic regions AP and Latin America. During the long-term follow-up (from Year 2 post last injection and beyond), no SVCD were reported in the non-efficacy Phase I/II Studies CYD05, CYD22 and CYD28. In the 3 efficacy studies (Studies CYD57, CYD14 and CYD15), based on validated data collected during the long-term safety follow-up (Year 1 and Year 2 Hospital Surveillance for CYD57 and Year 1 Hospital Phase for Studies CYD14 and CYD15), results per age group showed that, there was no evidence of excess of hospitalised VCD cases including SVCD cases in the Dengue Group compared to the Control Group in the subjects from 9 years of age, while there was a trend towards a higher incidence of hospitalised VCD and SVCD cases in subjects aged below 9 years.

There is no evidence, clinically, immunologically or virologically, that the disease in the Dengue Group is different to that observed with wild-type infection in Control Group. At the time of cut-off date for Hospital Surveillance/Phase data presentation (13 August 2015), preliminary data collected in Studies CYD57, CYD14 and CYD15 during uncompleted years of long term follow-up show the same trend, that is, a favourable benefit/risk ratio in subjects aged 9 years-old and above but an increased risk of hospitalised VCD including severe in subjects below 9 years of age.

9. First round benefit-risk assessment

9.1. First round assessment of benefits

Table 10: Assessment of benefits

Benefits	Risks and Uncertainties
The global incidence of dengue has grown dramatically in recent decades and half of the world's population is now considered at risk of infection by the dengue viruses. Around 500,000 hospitalisations are reported each year, and around 20,000 cases would result in death. School age children and young adults represent a population at significant risk of dengue disease in endemic countries. This vaccine appears to have efficacy in decreasing the incidence of dengue infection, associated hospitalisations and deaths. Two pivotal Phase III efficacy studies were conducted during the clinical development of the CYD dengue vaccine: CYD14 and	Considering the efficacy of the CYD dengue vaccine in populations from 9 years, VE was demonstrated in both studies with 67.8% and 64.7% in CYD14 and CYD15 respectively (meta-analysis showing overall efficacy of 65.6% in the 9 to 16 years population) against any serotype after at least 1 injection of the CYD dengue vaccine (FASE) during the first 25 months of the studies. Significant VE was also observed in preventing the occurrence of VCD case due to each serotype after at least 1 injection of the CYD dengue vaccine. Efficacy varied according to the serotype: moderate efficacy was observed for serotypes 1 and 2 and high efficacy was observed for serotypes 3 and 4.

Benefits	Risks and Uncertainties
CYD15. Each individual Phase III efficacy study was sufficiently powered to demonstrate significant efficacy of the CYD dengue vaccine in preventing the occurrence of VCD cases due to any serotype after 3 injections.	In dengue non-immune subjects at baseline, VE was inconclusive due to the limited number of cases in individual studies. The meta-analysis pooling results from CYD14 and CYD15 showed an effect with a VE estimate at 52.5% (95% CI: 5.9; 76.1); indicating a benefit in this population. The data generated is based on a 3-dose schedule administered 6 months apart. It was not possible to explore the efficacy of only 1 or 2 injections over a long period of time although efficacy was observed between injections. Vaccine efficacy was influenced by several factors. At the study level, the distribution of serotypes in the region or country at the time of the clinical study influenced efficacy outcomes: when serotype 2 predominated, overall efficacy was lower. At an individual level, the subjects' age at vaccination, previous exposure to dengue (immune status to dengue at baseline), and level of the response to the vaccine all had an effect on efficacy outcomes. Age can be considered as a key factor in predicting VE, with VE increasing with age increase. The efficacy data described is based on 25-month follow-up of the Active Phase of the 2 Phase III efficacy studies (up to 13 months after completion of the 3-dose vaccine regimen). During this time period, efficacy persisted with no evidence of waning. Although efficacy has not been evaluated in adults, immunogenicity data from studies conducted in adults aged 18 to 45 years in AP (CYD22, CYD47) suggest that adults have a high level of seropositivity and respond well to the vaccine schedule used in the efficacy studies. Indeed, post- injection 3 Ab levels are generally higher than those seen in CYD14 and CYD15 where efficacy was demonstrated. This 'bridging' of immunogenicity data from the efficacy studies to immunogenicity data in adults aged 18 to 45 years showed that levels of titres should be predictive of protection in this population supporting the indication for prevention of dengue disease in an adult aged 18 to 45 years living in endemic area.

Benefits	Risks and Uncertainties
	Immunogenicity bridging data was not available for the 46 to 60 years old population in endemic regions, but the Applicant's conclude that 46 to 60 years adults in endemic regions would have a comparable safety and immunogenicity profile to the 18 to 45 years population in the same endemic regions similarly as what is observed in non-endemic regions. In addition the immune response in terms of GMTs is higher in endemic regions than in non-endemic regions. Therefore, 46 to 60 years adults in endemic regions are expected to have a similar VE than 18 to 45 years adults in the same regions, which is considered to be similar to VE demonstrated in adolescents. Although this data is not yet available and is basely solely on theoretical extrapolation. At the time of the current application, no data on the long-term efficacy of the vaccine is available in the target population for use. Long-term protection from dengue will be evaluated through Post Approval Effectiveness studies with a follow-up of 5 years as described in the RMP. Analysis from data collected in subjects from 9 years of age in CYD14 and CYD15 during the first year of Hospital Phase and from the first 2 years of CYD57 (long-term follow-up of CYD23) showed no trend to increased risk of hospitalised (severe and non-severe) VCD cases. No studies to evaluate the value of a booster dose have been conducted to date. However administration of a booster dose will be evaluated in follow-up studies from Phase II in endemic countries in Latin America and AP, in subjects aged 9 years and above at inclusion in the Phase II studies, who will be asked to participate to new studies to receive a booster injection around 5 years after the last injection (CYD63 and CYD64).

9.2. First round assessment of risks

Table 11: Assessment of risks

Risks	Strengths and Uncertainties
Risk of AEs, SAES, ADRs related to vaccine. Risk of unacceptable reactogenicity profile. Possible increase in VCD cases requiring hospitalisation (severe and non-severe) in subjects aged 2 to 8 years (as seen in CYD14 and CYD23) Hospital Phase, that is, potential risk of increase in severity of dengue disease in this age group.	The safety data is available for approximately 28,600 subjects aged 9 months to 60 years who received at least 1 injection of the final formulation, regardless of the schedule. Among these subjects, 21,215 subjects were in the target age indication (9 to 60 years of age. The majority of the subjects are children and adolescents with 1982 adults aged 18 to 60 years of which 241 were over 45 years receiving at least one dose. The majority of subjects have been followed for safety for at least 1 year while all of the subjects enrolled in the 3 efficacy studies will be evaluated for safety and the occurrence of SAEs (all SAEs in CYD14 and CYD15 and related SAEs in CYD57) and hospitalised VCD for 5 years post-injection 3 with the provision of regular safety reports in an ongoing basis. No safety concerns were identified from the review of SAEs from the long-term follow-up of the CYD dengue vaccine clinical studies. In particular no related SAEs have been reported during the long-term follow-up, although it is still continuing. The methodology and outcome measures for the safety database were age appropriate and similar across all clinical studies so that data could be pooled for analysis which increased the power for the detection of safety signal. The data demonstrated that the reactogenicity profile after any injection of the CYD dengue vaccine is similar to licensed vaccines used in the age groups that have been studied and also similar when compared to placebo. During the Active Phase observation period of the Phase III efficacy studies, rates of severe VCD cases and hospitalised VCD cases in subjects from 9 years were significantly lower in the vaccinated treatment groups. From the analysis of the first year of Hospital Phase of CYD14 and CYD15, there is no increased risk of hospitalised VCD cases

Risks	Strengths and Uncertainties
	(including severe) in the 9 to 16 year-old population, nor in the first 2 years of Hospital Phase of CYD57 in subjects aged 9 to 11 years. This continues to be closely monitored in the long-term follow- up of CYD14, CYD15 and CYD57 (Hospital Phase) which will continue for 5 years. Post-approval effectiveness studies will also address the potential risk of increased severity of disease for the CYD dengue vaccinees in the target populations for licensure with studies designed with 5 years duration of follow-up.

9.3. First round assessment of benefit-risk balance

Data from the clinical development of the CYD dengue vaccine has shown that with a 3-dose regimen administered 6 months apart the vaccine is efficacious at the prevention of dengue disease in the subjects aged 9 to 16 years. Efficacy was observed against each of the 4 serotypes with high efficacy seen against severe VCD cases and hospitalised VCD cases over a 25-month observation period. The high post-injection titres seen in adults living in endemic areas in Asia allow us to theoretically bridge immunologically to an adult population.

There are no safety concerns surrounding the reactogenicity and AE profile of the candidate vaccine in the cumulative data provided. Overall, in the long-term follow-up data during the Hospital Phase across the 3 studies, no evidence of increased severity of dengue disease or increase in frequency of hospitalised Dengue cases has been observed in the 9 to 16 year olds. From this, the benefit/risk balance of the CYD dengue vaccine is positive.

10. First round recommendation regarding authorisation

The evaluator would recommend registration for an indication for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in individuals 9 through 60 years of age living in endemic areas.

11. Clinical questions

At the completion of the second round evaluation, the following clinical question was sent to the sponsor for consideration by the Delegate:

- TGA has noted a number of publications by Halstead and co-authors and also recently by Ferguson et al. raising concerns about the safety of dengue vaccine including the proposition that:

  The combination of poor protection against DENV infection of individuals with circulating DENV antibodies (monotypic immune equivalents) satisfies the known preconditions for antibody-dependent enhancement of infection.

  The papers include:

- Halstead SB (2016). Licensed dengue vaccine: public health conundrum and scientific challenge. Am. J. Trop. Med Hyg. 95(4): 741-745.
- Halstead SB (2016) Critique of World Health Organisation recommendation of a dengue vaccine. The Journal of Infectious Diseases. 214:1793-5.
- Halstead SB (2016). Dengue vaccines: Are they safe for travellers? Travel Med Infect Dis 14(4): 378-383.
- Aguiar M, Stollenwerk N and Halstead SB (2016). The risks behind Dengvaxia recommendation. Lancet Infect Dis 16: 882-883.
- Ferguson NM et al (2016). Benefits and risks of the Sanofi-Pasteur dengue vaccine: modeling optimal deployment. Science 353: 1033-1036

Your company is invited to provide a response to the concerns raised in these papers.

12. Second round evaluation of clinical data

No new clinical data submitted in the sponsor's response. PI and CMI have been amended in the sponsor's response to address first round evaluation comments. A clinical question was raised at the completion of second round evaluation.

13. Second round benefit-risk assessment

No change from first round.

14. Second round recommendation regarding authorisation

No change from first round.

15. Safety related request

15.1. Submission type

These applications were for a Safety Related Request (SRR) requiring evaluation of data and Minor Editorial Changes (MEC) to the PI.

- PM-2017-04923-1-2
- PM-2017-04924-1-2.

15.2. Background

15.2.1. Clinical rationale

The purpose of the SRR and MEC applications is to update PI to include results of a supplemental exploratory analysis aimed at evaluating the safety and efficacy of Dengvaxia according to dengue serostatus prior to vaccination.

15.2.2. Regulatory history

Dengvaxia was registered by TGA in July 2017. Dengvaxia has not been marketed in Australia.

Marketing Authorisation Applications for Dengvaxia have been submitted in several dengue endemic countries from January 2015. The priority for submission was given to the countries with the highest disease burden. At the time of the Pre-ACV Response, Dengvaxia has been approved in a total of 16 dengue endemic countries including Mexico, The Philippines, Brazil, El Salvador, Costa Rica, Guatemala, Indonesia, Peru, Bolivia, Singapore, Cambodia, Thailand, Paraguay, Venezuela, Argentina and Malaysia.

15.3. Supporting evidence

- Update of the PI of Dengvaxia including an additional warning based on new clinical data in individuals who have not been previously infected by dengue virus.

15.3.1. Background

Two pivotal Phase III efficacy studies (CYD14 and CYD15) and a proof of concept Phase IIb efficacy study (CYD23/57) were conducted during the clinical program of the CYD dengue vaccine. The Phase IIb study including the associated long term follow-up period is completed. The 6th year and last year of follow-up after the first injection is currently ongoing in both Phase III efficacy studies.

Results from the Phase III efficacy studies (CYD14 in Asia and CYD15 in Latin America) also showed that vaccine efficacy (VE) was impacted by prior exposure to wild type dengue infection. Immunogenicity subsets comprised approximately 20% of the overall population in CYD14 and approximately 10% in CYD15. In the "immunogenicity subset" for whom serostatus was evaluated at baseline, efficacy was higher in those previously exposed to dengue infection (referred to as "seropositive" and defined as plaque reduction neutralization test (PRNT) ≥ 1:10 to any dengue serotype at baseline) than in those who were dengue-naïve at baseline (referred to as "seronegative"). Pooled VE against Virologically confirmed dengue (VCD) cases in subjects aged ≥ 9 years at enrolment across these 2 pivotal efficacy studies was 81.9% (95% CI: 67.2; 90.0) among subjects ≥ 9 years of age classified as seropositive at baseline compared to 52.5% (95% CI: 5.9; 76.1) among seronegative subjects.

During the first year of the Hospital Phase of CYD14 (i.e. during the third year after the first injection), the Phase III efficacy trial conducted in Asia, there was an imbalance and a significant increased risk of hospitalized and/or severe symptomatic VCD in the youngest vaccine recipients (subjects aged 2 to 5 years at enrolment). The observation of an 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.

In order to further evaluate the safety and efficacy of the CYD dengue vaccine according to dengue serostatus prior to vaccination; the sponsor has conducted a supplemental exploratory analyses using blood samples for all study participants collected at Month 13 (M13), 1 month after the third injection of CYD dengue vaccine. A positive PRNT assay at Month 13 can be the result of either prior dengue exposure or CYD dengue vaccination. The sponsor has used a dengue anti-non-structural protein 1(NS1) IgG ELISA assay as a surrogate of baseline serostatus. The NS1 protein is not conserved between dengue virus and yellow-fever virus and anti-NS1 seropositivity initially considered a result of prior dengue exposure.

Comment: Some misclassification of baseline sero-status associated with CYD vaccine effect on the Dengue anti-NS1 readout at Month 13 was identified in the supplemental exploratory analyses.

The dengue NS1 protein is a conserved glycoprotein that is secreted from dengue infected cells in-vitro and is detected within the serum of infected patients. The test has been demonstrated to be specific to dengue and sensitive in most studies of sera from different populations.

The dengue NS1 ELISA kit was obtained commercially from BioRadassay. Test method used CVD and Focus Diagnostics Test Procedures. In the initial analyses, seronegativity is defined as an anti-NS1 titre < 9 EU/mL and seropositivity as an anti-NS1 titre ≥ 9 EU/mL.

15.3.2. Supplemental exploratory analyses

The analyses of serostatus at M13 determined by anti-NS1 IgG ELISA was considered useful for expanding existing data on both efficacy and dengue hospitalisation and/or severe dengue in CYD dengue vaccine efficacy studies from Month 13 to Month 60 to 72 and for symptomatic VCD cases to M25.

Two clinical study reports were submitted. NS1 CSR#1 Version 1.0 dated 30 November 2017 and NS1 CSR #2 (NS1 extension study) Version 1.0 dated 5 December 2017.

These are additional reports to Phase IIb and 3 study reports listed below:

- CYD14 Interim CSR Version 4 dated 12 October 2017
- CYD15 Interim CSR Version 3.0 dated 19 October 2016
- CYD23 Final CSR Version 2 dated 25 October 2015
- CYD57 Final CSR Version 2.0 dated 20 October 2016.

Study signature was the sponsor's Responsible Medical Officer.

The trials were performed in compliance with GCP.

The NS1 Extension analysis was developed to address potential limitations identified in NS1 CSR#1 that included excess misclassification of baseline serostatus associated with CYD vaccine effect on the Dengue anti-NS1 readout at M13, potentially imperfect representativeness of the original sub-cohort due to the enrolment period of the immunogenicity subsets in CYD14 and CYD15 being shorter than the enrolment period of the entire corresponding studies, and gaps due to a lack of accounting for M0-M13 cases.

The evaluation of dengue outcomes according to dengue serostatus was based on the analysis of blood samples collected from subjects in 3 vaccine efficacy (VE) trials (CYD14, CYD15, and CYD23/57). In a subset of subjects, designated as the "immunogenicity subset," blood samples were also collected at baseline prior to vaccination. In CYD14 and CYD15 these subjects were randomly selected (n = 2000 per study) and in CYD23, the 300 subjects were selected non-randomly to provide the baseline blood samples.

The case-cohort study design utilized for the NS1 analyses includes the selection of a random sample of subjects, referred to as the sub-cohort, from the entire study population. NS1 CSR#1 included a random subset of approximately 10% of subjects that were enrolled over the period required to recruit the immunogenicity subset. NS1 CSR #2 includes the sub-cohort from NSR CSR#1 and in addition a random subset of approximately 10% of subjects enrolled outside the immunogenicity subset recruitment period referred to as the "expanded sub-cohort".

Dengue serostatus in the extended analysis was classified using baseline (M0) plaque reduction neutralization test (PRNT)50 (either measured [from subjects included in the immunogenicity subset] or imputed [from subjects for whom no baseline PRNT50 data was available]) and anti-NS1 IgG ELISA levels measured at M13 in subjects in the expanded case-cohort. NS1 CSR#1 used an anti-NS1 IgG ELISA seropositivity threshold of ≥ 9 EU/mL at M13. (Subjects with symptomatic VCD before M13 were excluded from CSR#1). NS1 CSR# 2 included analyses with seropositivity thresholds of ≥ 9 EU/mL and > 20 EU/mL.

NS1 CSR#1 and NS1 CSR #2 had different primary objectives and different statistical methods for the primary objective. There were numbers of secondary and exploratory endpoints common or overlapping in these studies.

NS1 CSR#1 had a primary objective to compare the risk of dengue hospitalization and/or severe dengue occurring after M13 (including Active and Hospital Phase) in CYD dengue vaccine versus control study subjects aged ≥ 9 years at enrolment and classified as dengue seronegative at M13.

Statistical methods for the primary objective estimated using a modified Cox regression model, including the vaccine group as co-variate, the risk of dengue hospitalization and/or severe dengue in CYD dengue vaccine versus placebo control study participants. Similar modified Cox regression models evaluated risk modification by age and serostatus at M13.

NS1 CSR #2 had a primary objective to compare the risk of dengue hospitalization occurring after M0 or after M13 (including Active and Hospital Phase/Surveillance Expansion Period) in CYD dengue vaccine versus control study subjects aged ≥ 9 years at enrolment and classified as dengue seronegative.

Statistical methods for the primary objective involved prediction of M0 PRNT50 serostatus by multiple imputation and Super-Learner methods. For the Super-learner method, by subject probabilities of being seropositive/seronegative were estimated for all subjects in the expanded case-cohort and the immunogenicity subset. Risk of dengue hospitalization was then estimated by using inverse probability weighting integrated into a TMLE framework. 4 sets of analyses were produced:

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

A modified Cox model, including the vaccine group as covariate, was used to calculate the hazard ratio for the primary endpoint.

Secondary objectives in NS1 CSR#1 included 5 safety objectives related to risk of dengue hospitalisation and/or severe dengue occurring after M13 in various age groupings and according to dengue serostatus.

6 secondary efficacy objectives in NS1 CSR#1 related to occurrence of symptomatic VCD cases between M13 and end of Active Phase in various age groups, and by dengue serotypes.

There were 13 exploratory objectives in CSR#1.

In CSR#2 safety objectives were identified:

- To compare the risk of dengue hospitalization occurring after M0 or after M13 (including Active and Hospital Phase) in CYD dengue vaccine versus control study subjects of any age who were classified as dengue seronegative.
- To compare the risk of dengue hospitalization occurring after M0 or after M13 (including Active and Hospital Phase) in CYD dengue vaccine versus control study subjects who were younger than 9 years of age at enrolment and classified as dengue seronegative.

In CSR#2 efficacy objectives were to evaluate the efficacy of the CYD dengue vaccine in preventing the occurrence of symptomatic VCD cases between M0 and the end of Active Phase and between M13 and the end of Active Phase, regardless of severity and dengue serotype, in subjects aged ≥ 9 years at enrolment who were classified as dengue seronegative, in subjects of any age who were classified as seronegative and in subjects younger than 9 years of age.

15.3.3. Results for NS1 CSR#1

15.3.3.1. Subjects included in the analyses for different endpoints

The sub-cohort included 3246 subjects across all studies.

There were 537 cases (271 for CYD14, 97 for CYD15, and 169 for CYD57) of dengue hospitalization and/or severe dengue that occurred after M13 up to the cut-off dates.

There were 113 cases (78 for CYD14, 21 for CYD15, and 14 for CYD57) of severe dengue that occurred after M13 up to the cut-off dates.

There were 653 cases (237 for CYD14 and 416 for CYD15) of symptomatic VCD that occurred between M13 and the end of Active Phase.

15.3.3.2. Baseline demographics

There were 3246 subjects in the sub-cohort. 48.8% were male, 51.2% were female and mean age was 10.7 years. The proportion of subjects aged ≥ 9 years was 77.1%. Baseline demographics were similar in CYD Dengue and control groups.

15.3.3.3. Dengue serostatus

Based on subject serostatus classified by anti-NS1 ELISA with threshold of 9 EU/mL at M13 the proportion of all subjects classified as seronegative was 21.2% (790/3731).

For subjects in the sub-cohort (N = 3246), 618 subjects (19%) of any age were classified as seronegative with more classified as seronegative in the Placebo Group (22.1%, 237/1071) than in the CYD Dengue Vaccine Group (17.5%, 381/2175). The ratio of CYD: Placebo in seronegative subjects was 1.61, unexpectedly lower than the randomization of 2:1 observed for the initial source population.

The overall percentage agreement between $PRNT_{50}$ 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).

15.3.3.4. Results for the primary endpoint

In subjects ≥ 9 years of age classified as seronegative by anti-NS1 assay at M13, no significant increase in the risk of dengue hospitalization and/or severe dengue was observed over the entire study period after M13 (HR: 0.957 [95% CI: 0.540, 1.695]). The HR was 1.956 (95% CI: 0.631; 6.061) for CYD15, 0.699 (95% CI: 0.302; 1.616) for CYD14, and 0.657 (95% CI: 0.171; 2.524) for CYD23/57.

The risk of severe dengue occurring over the entire study period after M13 showed 8 cases in the Dengue Group (N = 230) and 1 case in the Placebo group (N= 131) with an HR of 4.404 (95% CI: 0.546, 35.506).

15.3.3.5. Secondary and exploratory safety endpoints

For seronegative subjects across all age groups, classified by the anti-NS1 assay at M13, in the risk of dengue hospitalisation and/or severe dengue after M13, the HR pooled across all studies over the entire study period was 1.656 (95% CI: 1.159, 2.367).

For seropositive subjects aged < 9 years, classified by the anti-NS1 assay at M13, in the risk of hospitalisation and/or severe dengue, the HR pooled from CYD14 and CYD23/57 over the entire study period was 2.315 (95% CI: 1.445, 3.708).

The association between treatment group and dengue hospitalization and/or severe dengue was significantly modified by serostatus ($p < 0.001$) on the pooled estimates of risk for subjects aged ≥ 9 years, < 9 years, or of any age.

For seropositive subjects aged < 6 years, classified by the anti-NS1 assay at M13, in the risk of Dengue hospitalisation and/or severe dengue the pooled HR was 3.146 (95% CI: 1.492, 6.636). In seronegative subjects aged < 9 years, there were 17 severe cases in the CYD Dengue Group (N = 151) and 3 cases in the Placebo Group (N = 106) and an HR of 3.942 (95% CI: 1.130, 13.746).

For seropositive subjects ≥ 9 years, classified by the anti-NS1 assay at M13, in the risk of Dengue hospitalisation and/or severe dengue the HR pooled from all studies over the entire study

period was 0.297 (95% CI: 0.217, 0.406). HRs significantly lower than 1 were observed in dengue seropositive subjects aged < 9 years and for analyses including subjects of any age.

For seronegative subjects > 9 years, classified by the anti-NS1 assay at M13, against symptomatic VCD between M13 and end of active phase the VE pooled from both CYD14 and CYD 15 was 11.2% (95% CI: -38.2, 42.9).

For seronegative subjects of any age, the overall VE was 7.1% (95% CI: -31.5, 34.4) while in subjects aged < 9years, the VE in CYD14 (there were no subjects aged < 9 years in study CYD15) was -0.2% (95% CI: -76.0, 42.9).

The association between treatment group and occurrence of symptomatic VCD was significantly modified by dengue serostatus ($p < 0.001$) on the pooled estimates of VE in seronegative subjects aged ≥ 9 years, aged < 9 years, or of any age.

For seropositive subjects aged ≥ 9 years the VE pooled from both CYD14 and CYD15 was 71.3% (95% CI: 64.2, 77.1).

15.3.4. Results for NS1 CSR#2

15.3.4.1. Subjects included in the analyses for different endpoints

The expanded sub-cohort included 3,578 subjects across all studies and included between 8.7% and 10.7% of individual study cohorts.

There were 644 cases of dengue hospitalization occurring after M0, 142 cases of severe dengue (IDMC definition) occurring after M0, and 1,258 cases of symptomatic VCD occurring between M0 and the end of Active Phase.

15.3.4.2. Baseline demographics

In the expanded sub-cohort, 47.8% were male and 52.2% were female with a mean age of 10.9 years. The proportion of subjects aged ≥ 9 years was 78.7%. The distribution of Baseline demographics in the sub-cohort was balanced between the CYD Dengue and Control Group.

15.3.4.3. Dengue serostatus

Serostatus determined by PRNT50 at M0

Subjects in the sub-cohort were classified as seropositive or seronegative by PRNT50 at baseline (M0). The serostatus was either measured (for subjects included in the immunogenicity subset) or imputed (for subjects in the expanded case-cohort, but not in the immunogenicity subset). Among all subjects, the percentage of seronegative subjects determined by multiple imputation was 24.5% (875.7/3578).

Overall, the CYD: Placebo ratio by $PRNT_{50}$ serostatus with the multiple imputation approach was 1.85 for seronegatives and 2.05 for seropositives and ranged between 1.61 and 2.36 depending upon trial and age strata.

Serostatus determined by anti-NS1 ELISA at M13

Subjects in the sub-cohort were classified by anti-NS1 titre at M13 excluding VCD cases between M0 and M13 based upon two thresholds (9 EU/mL and 20 EU/mL). The overall proportion of subjects of any age classified as seronegative by the anti-NS1 assay at M13 (Threshold 9) in the entire sub-cohort was 23.4% (784/3356) and in subjects aged ≥ 9 years, it was 18.9% (501/2638). The overall proportion of seronegative subjects of any age in the CYD Dengue Group was 65.3% (512/784) and 34.7% (272/784) in the Placebo Group.

Overall, across subjects of any age, the ratio of CYD: Placebo was 1.88 in seronegative subjects and 2.13 in seropositive subjects.

When analysed using a threshold of 20 EU/mL, the overall proportion of seronegative subjects in the entire sub-cohort was 28.3% (953/3356) for subjects of any age and 22.7% (598/2638) in subjects ≥ 9 years of age. Across subjects of any age, the ratio of CYD: Placebo was 1.94 in seronegative subjects and 2.12 in seropositive subjects.

Concordance

Among subjects in the immunogenicity subset there was 88.5% agreement between PRNT50 at M0 and anti-NS1 ELISA (Threshold 9) at M13 for classification of serostatus (kappa coefficient 0.69 (95% CI: 0.67, 0.72). The concordance was slightly higher with anti-NS1 ELISA (Threshold 20).

In the immunogenicity subset, a statistically significant ($p < 0.001$) increase in the anti-NS1 GMTs post injection (M13) to pre-vaccination/injection (M0) was observed in the CYD Vaccine Group (geometric mean titre ratio [GMTR]: 1.28) compared to the Placebo Group (GMTR: 0.99) in subjects without VCDs.

There was 92% agreement overall original and new anti-NS1 ELISA readouts with kappa coefficient 0.788 (95% CI: 0.766, 0.809), overall. Concordance was lower in the CYD Vaccine Group (kappa coefficient: 0.758 [95% CI: 0.730, 0.786]) than in the Placebo Group (kappa coefficient: 0.842 [95% CI: 0.810, 0.874]). More subjects classified as seropositive by the original readout (n = 298) were classified as seronegative by the new readout than vice-versa (n = 40). Among these 298 subjects classified as seronegative with the new readout, the majority (222 subjects) were in the CYD Dengue Vaccine Group.

15.3.4.4. Impact of CYD vaccine on anti-NS1 Titres at M13

In the immunogenicity subset, among subjects classified as seronegative at M0 by anti-NS1 readouts (Threshold 9), 19.9% (139/699) were misclassified as seropositive using anti-NS1 readouts at M13 (Threshold 9) in the CYD Vaccine Group. This misclassification was significantly higher ($p = 0.0009$) than that observed in the Placebo Group (11.6%, 39/337).

The misclassification in the CYD Vaccine Group was higher among subjects with hospitalized dengue (26.9%, 7/26) compared to those without hospitalized dengue (19.6%, 132/673), but lower in subjects with symptomatic VCD (7.1%, 1/14) compared to those without a symptomatic VCD (20.2%, 138/684). No differential misclassification between cases and non-cases of symptomatic VCD was observed in the Placebo Group.

In the immunogenicity subset, among subjects classified as seronegative by multiple imputation, 79.1% were seronegative by measured $PRNT_{50}$ and 20.9% were seropositive by measured $PRNT_{50}$.

15.3.4.5. Results for the primary endpoint

The risk of dengue hospitalisation in subjects > 9 years at enrolment after M0 or M13 classified as seronegative by PRNT50 at M0 (measured or imputed is summarised in Table 11).

Table 12: Risk of dengue hospitalization occurring after M0 or M13 by time period in subjects ≥ 9 years at enrolment and classified as dengue seronegative by PRNT50 at M0 - all studies (measured/imputed)

	Number of Subjects with Cases		Risk of dengue hospitalization		
	Vaccine Group n (N)	Placebo Group n (N)	Hazard Ratio/Relative Risk	95% Confidence Interval	p-value
All studies					
TMLE Month (M) 0 onwards	78.1 (3597.4)	31.7 (2009.7)	1.51	(0.73,3.11)	0.263
MI M0 onwards	64.2 (375.1)	25.3 (207.2)	1.412	(0.743, 2.682)	0.287
TMLE M13 onwards	54.3 (3374.7)	22.3 (1834.6)	1.45	(0.68;3.09)	0.335
MI M13	56.4 (356.2)	20.3 (189.9)	1.502	(0.785, 2.872)	0.216
CYD14+CYD15					
TMLE M0 onwards	55.4 (3386.5)	26.0 (1959.5)	1.35	(0.65,2.84)	0.422
MI M0 onwards	53.5 (353.5)	20.9 (193.8)	1.404	(0.704, 2.800)	0.330
TMLE M13 onwards	49.5 (3186.1)	17.7 (1785.7)	1.67	(0.69, 4.03)	0.254
MI M13 onwards	47 (335.8)	16.3 (176.5)	1.528	(0.739, 3.160)	0.250
CYD14					
TMLE M0 onwards	33.1 (706.8)	17.6 (321.2)	1.11	(0.56,2.18)	0.766
MI M0 onwards	27.8 (77.4)	13.5 (32.8)	0.921	(0.412, 2.060)	0.841
TMLE M13 onwards	29.6 (666.3)	13.8 (282.8)	1.13	(0.52; 2.43)	0.764
MI M13 onwards	24.2 (75.3)	11.7 (29.7)	0.863	(0.363, 2.054)	0.739
CYD15					
TMLE M0 onwards	22.3 (2679.6)	8.4 (1638.4)	1.68	(0.22,12.69)	0.613
MI M0 onwards	25.7 (276.1)	7.4 (161)	2.174	(0.497, 9.512)	0.290
TMLE M13 onwards	19.9 (2519.8)	3.9 (1502.9)	2.95	(0.11; 77.20)	0.516
MI M13 onwards	22.8 (260.5)	4.6 (146.8)	2.921	(0.755, 11.304)	0.119
CYD23/57					
MI M0 onwards	10.7 (21.6)	4.4 (13.4)	1.695	(0.216, 13.302)	0.606
MI M13 onwards	9.4 (20.4)	4 (13.4)	1.716	(0.204, 14.438)	0.609

For all MI approaches, n represents the number of subjects fulfilling the item listed and N represents the total number of subjects selected in sub-cohort; n and N are average numbers from 10 iterations of multiple imputations. For all TMLE approaches, n represents the number of arm-specific events in a given sub-cohort (whether or not M13 anti-NS1 titres were measured) where the expectation averages out uncertainty in the baseline PRNT sero-probabilities and N represents the expected number of individuals in that arm-specific sub-cohort. Study group classified as treated (Subjects classified as CYD Dengue Vaccine Group if received at least 1 injection of CYD dengue vaccine)

The HR/RR pooled from all studies (CYD14, CYD15 and CYD57) was consistent across all methods and greater than 1 but not statistically significant. The risk estimates ranged from 1.002 by anti-NS1 M13 (Threshold 20) to 1.51 by TMLE M0. When analysed by individual study, the risk of dengue hospitalization was higher in CYD15 (HR/RR ranged between 1.336 by anti-NS1 M13 [Threshold 20] to 2.95 by TMLE M13) than in CYD14 (HRs ranged between 0.716 by anti-NS1 M13 [Threshold 20] and 1.13 by TMLE M13) regardless of the method used.

Table 13: Risk of dengue hospitalization occurring after M13 by time period in subjects aged ≥ 9 years and classified as seronegative by measured NS1 at M13 - all studies

	Number of Subjects with Cases		Risk of dengue hospitalization		
	Vaccine Group n (N)	Placebo Group n (N)	Hazard Ratio	95% CI	p-value
All studies					
Threshold 9 EU/mL	56 (330)	20 (171)	1.455	(0.851, 2.488)	0.171
Threshold 20 EU/mL	69 (393)	36 (205)	1.002	(0.651, 1.544)	0.992
CYD14					
Threshold 9 EU/mL	23 (63)	11 (27)	0.907	(0.400, 2.060)	0.816
Threshold 20 EU/mL	29 (81)	17 (33)	0.716	(0.356, 1.443)	0.351
CYD15					
Threshold 9 EU/mL	25 (246)	5 (130)	2.631	(0.988, 7.002)	0.053
Threshold 20 EU/mL	30 (287)	12 (155)	1.336	(0.667, 2.675)	0.414
CYD14+CYD15					
Threshold 9 EU/mL	48 (309)	16 (157)	1.525	(0.843, 2.758)	0.163
Threshold 20 EU/mL	59 (368)	29 (188)	1.028	(0.640, 1.653)	0.908
CYD23/57					
Threshold 9 EU/mL	8 (21)	4 (14)	1.287	(0.346, 4.784)	0.706
Threshold 20 EU/mL	10 (25)	7 (17)	0.978	(0.335, 2.857)	0.967

Subjects with virologically confirmed dengue cases before M13 were excluded from the analyses n: number of subjects fulfilling the item listed. N: total number of subjects selected in sub-cohort. Study group classified as treated (Subjects classified as CYD Dengue Vaccine Group if received at least 1 injection of CYD dengue vaccine)

The risk of dengue hospitalisation occurring after M13 in seronegative by time periods in subjects > 9years is summarised.

Table 14: Risk of dengue hospitalization occurring after M13 by time period in subjects aged ≥ 9 years and classified as seronegative by measured NS1 at M13 - all studies

		Number of Subjects with Cases		Risk of dengue hospitalization		
		Vaccine Group n (N)	Placebo Group n (N)	Hazard Ratio	95% Confidence Interval	p-value
Active Phase						
	Threshold 9 EU/mL	11 (330)	4 (171)	1.434	(0.469, 4.385)	0.528
	Threshold 20 EU/mL	11 (393)	7 (205)	0.818	(0.325, 2.055)	0.669
Year 1 of Hospital Phase						
	Threshold 9 EU/mL	15 (330)	2 (171)	3.012	(0.954, 9.512)	0.060
	Threshold 20 EU/mL	19 (393)	6 (205)	1.441	(0.640, 3.245)	0.378
Year 2 of Hospital Phase						
	Threshold 9 EU/mL	15 (330)	5 (171)	1.457	(0.550, 3.860)	0.449
	Threshold 20 EU/mL	19 (393)	8 (205)	1.091	(0.526, 2.262)	0.815
Beyond Year 2 of Hospital Phase						
	Threshold 9 EU/mL	15 (330)	9 (171)	0.968	(0.399, 2.344)	0.942
	Threshold 20 EU/mL	20 (393)	15 (205)	0.808	(0.394, 1.658)	0.561

Subjects with virologically confirmed dengue cases before M13 were excluded from the analyses n: number of subjects fulfilling the item listed. N: total number of subjects selected in sub-cohort. Study group classified as treated (Subjects classified as CYD Dengue Vaccine Group if received at least 1 injection of CYD dengue vaccine)

In the pooled analysis of seronegative subjects aged ≥ 9 years, across all studies, the HR/RR for dengue hospitalization was < 1 during the Active Phase across all methods using PRNT50 at baseline (MI or TMLE, Table 6.3), but the HR was > 1 when estimated with anti-NS1 M13 (Threshold 9) to classify serostatus. None of the estimates in the Active Phase were statistically significant. The risk of dengue hospitalization increased during the Hospital Phase with HR/RR > 1 over the entire duration of the Hospital Phase for PRNT50-based methods. The HR/RR was > 2 during Y1 and Y2 of the Hospital Phase (based on TMLE and MI) and decreased beyond Y2 of the Hospital Phase to be close to 1. A similar trend was observed when estimating risk with anti-

NS1 at M13 to classify serostatus, but HR was close to neutral for estimates beyond Y2 of the Hospital Phase.

These trends are illustrated by the cumulative incidence curve for MI method from M0. The cumulative risk in the CYD Dengue Vaccine Group in seronegative subjects is higher than that in the Placebo Group and a crossing of the curves for CYD Dengue Group over the Placebo Group occurs around M30. The cumulative incidence curves based on other methods show a similar pattern with differences in the time point at which there is a crossing of the curves in seronegative CYD Dengue group over the seronegative Placebo Group.

Figure 4: Kaplan-Meier Curve of time to dengue hospitalization from M0 in subjects aged ≥ 9 years at enrolment - serostatus classified by PRNT at baseline (multiple imputation approach)

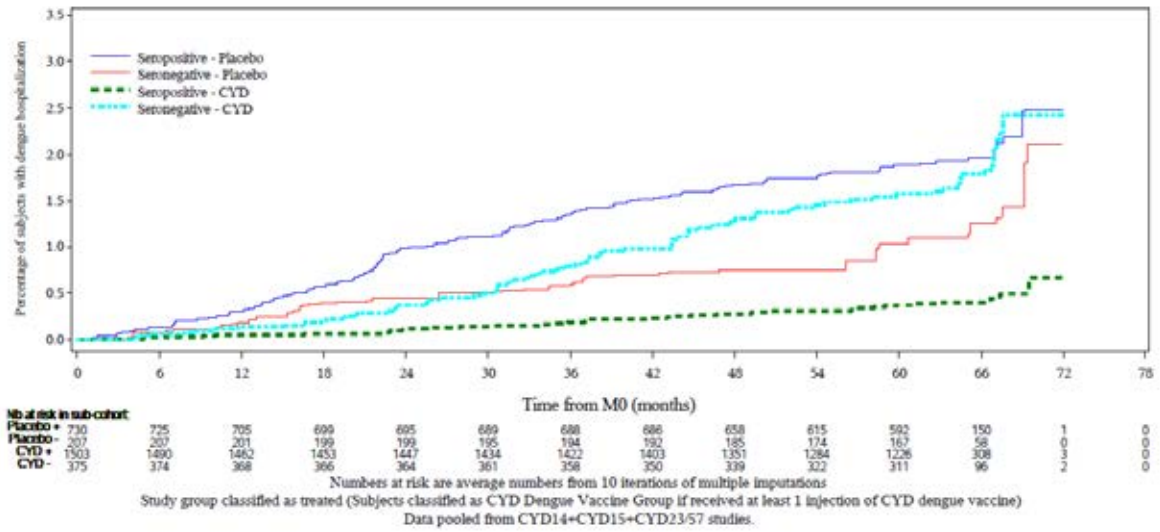
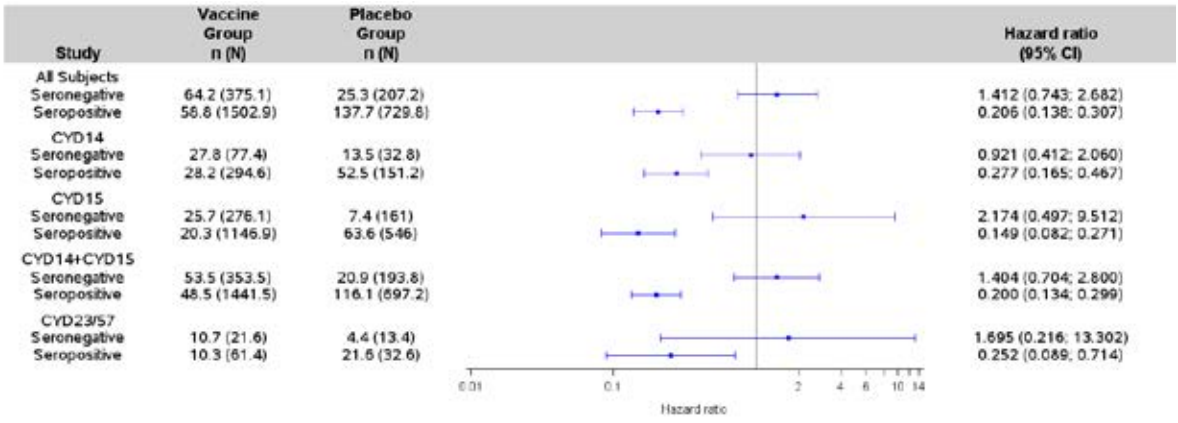


Figure 5: Risk of dengue hospitalization occurring after M0 in subjects aged ≥ 9 years at enrolment - serostatus classified by PRNT at M0



n: number of subjects fulfilling the item listed
N: total number of subjects enrolled in sub-cohort
n and N 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)

15.3.4.6. Secondary and exploratory objectives

The risk of dengue hospitalization after M0 or M13 in seronegative subjects of any age is summarized below.

Table 15: Risk of dengue hospitalization occurring after M0 or M13 in subjects of any age at enrolment and classified as dengue seronegative by PRNT50 imputed/predicted at M0 (measured/imputed)

	Number of Subjects with Cases		Risk of dengue hospitalization		
	Vaccine Group n (N)	Placebo Group n (N)	Hazard Ratio/Relative Risk	95% Confidence Interval	p-value
All studies					
TMLE Month (M) 0 onwards*	244.0 (5471.5)	65.5 (2968.2)	2.10	(0.94,4.70)	0.071
MI M0 onwards†	201.6 (567.9)	62.5 (307.8)	1.752	(1.138, 2.698)	0.012
TMLE M13 onwards‡	215.4 (5166.1)	54.6 (2734.6)	2.17	(0.82,5.75)	0.121
MI M13§	182.7 (541.5)	50.5 (285.2)	1.932	(1.220, 3.059)	0.006
CYD14+CYD15					
TMLE M0 onwards*	129.8 (4802.7)	50.9 (2693.4)	1.55	(0.98,2.47)	0.063
MI M0 onwards†	135.1 (495.2)	43.9 (268.3)	1.654	(1.047, 2.614)	0.031
TMLE M13 onwards‡	120.3 (4517.7)	35.9 (2454.5)	1.88	(1.10,3.22)	0.021
MI M13onwards§	119.1 (470.7)	32.6 (245.7)	1.917	(1.144, 3.213)	0.014
CYD14					
TMLE M0 onwards*	107.5 (2123.0)	42.5 (1055.0)	1.43	(0.92,2.21)	0.111
MI M0 onwards†	109.4 (219.1)	36.5 (107.3)	1.492	(0.932, 2.388)	0.095
TMLE M13 onwards‡	100.4 (1997.9)	32.0 (951.6)	1.59	(0.97,2.61)	0.063
MI M13 onwards§	96.3 (210.2)	28 (98.9)	1.663	(0.976,	0.061

				2.833)	
CYD15					
TMLE M0 onwards*	22.3 (2679.6)	8.4 (1638.4)	1.68	(0.22,12.69)	0.613
MI M0 onwards†	25.7 (276.1)	7.4 (161)	2.174	(0.497, 9.512)	0.290
TMLE M13 onwards‡	19.9 (2519.8)	3.9 (1502.9)	2.95	(0.11,77.20)	0.516
MI M13 onwards§	22.8 (260.5)	4.6 (146.8)	2.921	(0.755, 11.304)	0.119
CYD23/57					
MI M0 onwards†	66.5 (72.7)	18.6 (39.5)	2.020	(0.788, 5.175)	0.138
MI M13 onwards §	63.6 (70.8)	17.9 (39.5)	2.041	(0.809, 5.153)	0.127

For all MI approaches, n represents the number of subjects fulfilling the item listed and N represents the total number of subjects selected in sub-cohort; n and N are average numbers from 10 iterations of multiple imputations. For all TMLE approaches, n represents the number of arm-specific events in a given sub-cohort (whether or not M13 anti-NS1 titres were measured) where the expectation averages out uncertainty in the baseline PRNT seroprobabilities and N represents the expected number of individuals in that arm-specific sub-cohort. Study group classified as treated (Subjects classified as CYD Dengue Vaccine Group if received at least 1 injection of CYD dengue vaccine).

For pooled studies (CYD14, CYD15, CYD23/57) in subjects of any age, the HR for dengue hospitalization was > 1 with the MI approach for both M0 onward (HR: 1.752 [95% CI: 1.138, 2.698]) and for M13 onward (HR: 1.932 [95% CI: 1.220, 3.059]) and statistically significant (p = 0.012 and p = 0.006, respectively).

The risk of dengue hospitalization after M0 or M13 in seronegative subjects aged < 9 years is summarized below.

Table 16: Risk of dengue hospitalization occurring after M0 or M13 in subjects aged < 9 years at enrolment and classified as seronegative by $PRNT_{50}$ at M0 (measured/imputed)

	Number of Subjects with Cases		Risk of dengue hospitalization		
	Vaccine Group n (N)	Placebo Group n (N)	Hazard Ratio/Relative Risk	95% Confidence Interval	p-value
All studies					
TMLE Month (M) 0 onwards*	165.9 (1874.1)	33.8 (958.5)	2.48	(0.64, 9.54)	0.188

	Number of Subjects with Cases		Risk of dengue hospitalization		
	Vaccine Group n (N)	Placebo Group n (N)	Hazard Ratio/Relative Risk	95% Confidence Interval	p-value
MI M0 onwards†	137.4 (192.8)	37.2 (100.6)	1.949	(1.192, 3.186)	0.008
TMLE M13 onwards‡	161.1 (1791.4)	32.3 (900.0)	2.52	(0.55, 11.46)	0.232
MI M13§	126.3 (185.3)	30.2 (95.3)	2.204	(1.292, 3.758)	0.004
CYD14					
TMLE M0 onwards*	74.4 (1416.2)	25.0 (733.9)	1.66	(0.94, 2.95)	0.083
MI M0 onwards†	81.6 (141.7)	23 (74.5)	1.881	(1.051, 3.367)	0.034
TMLE M13 onwards‡	70.7 (1331.6)	18.2 (668.8)	1.97	(1.04, 3.75)	0.038
MI M13 onwards§	72.1 (134.9)	16.3 (69.2)	2.322	(1.175, 4.590)	0.016
CYD23/57					
MI M0 onwards†	55.8 (51.1)	14.2 (26.1)	2.059	(0.791, 5.357)	0.136
MI M13 onwards§	54.2 (50.4)	13.9 (26.1)	2.056	(0.806, 5.245)	0.130

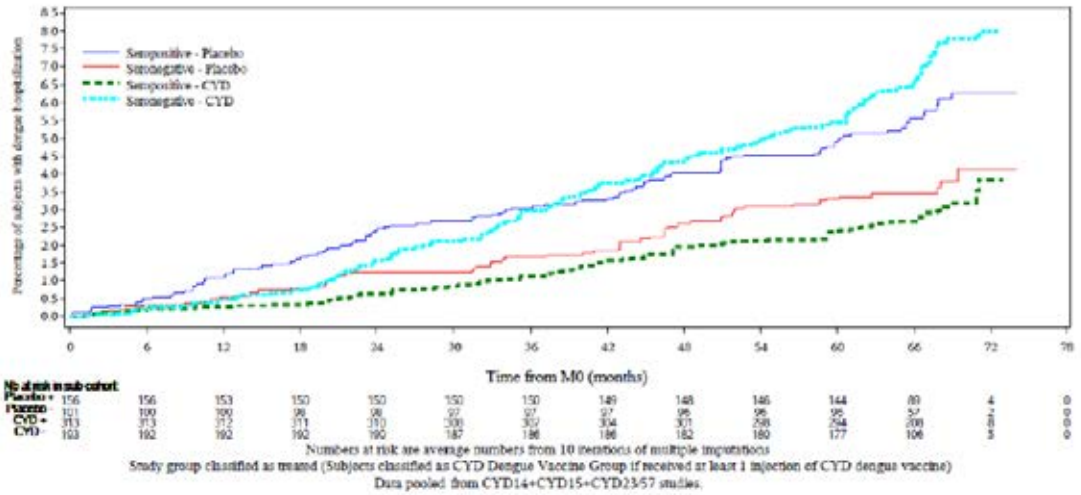
For all MI approaches, n represents the number of subjects fulfilling the item listed and N represents the total number of subjects selected in sub-cohort; n and N are average numbers from 10 iterations of multiple imputations. For all TMLE approaches, n represents the number of arm-specific events in a given sub-cohort (whether or not M13 anti-NS1 titres were measured) where the expectation averages out uncertainty in the baseline PRNT seroprobabilities and N represents the expected number of individuals in that arm-specific sub-cohort. Study group classified as treated (Subjects classified as CYD Dengue Vaccine Group if received at least 1 injection of CYD dengue vaccine).

For pooled studies (CYD14 and CYD23/57), the HR/RR was > 1.9 for all the TMLE and MI approaches from M0 and M13 onwards. The HRs from the MI method for M0 onward (1.949 [95% CI: 1.192, 3.186]) and for M13 onward (HR: 2.204 [95% CI: 1.292, 3.758]) were statistically significant (p = 0.008 and p = 0.004, respectively). Similar results were obtained in seronegative subjects by anti-NS1 titres with a threshold of 20 EU/mL.

When analysed by individual study, the HR/RR of dengue hospitalization in subjects aged < 9 years was > 1 in both CYD14 and CYD23/57 regardless of the calculation method (TMLE or MI) used and was statistically significant in CYD14 (except with the TMLE M0 method [p = 0.083]).

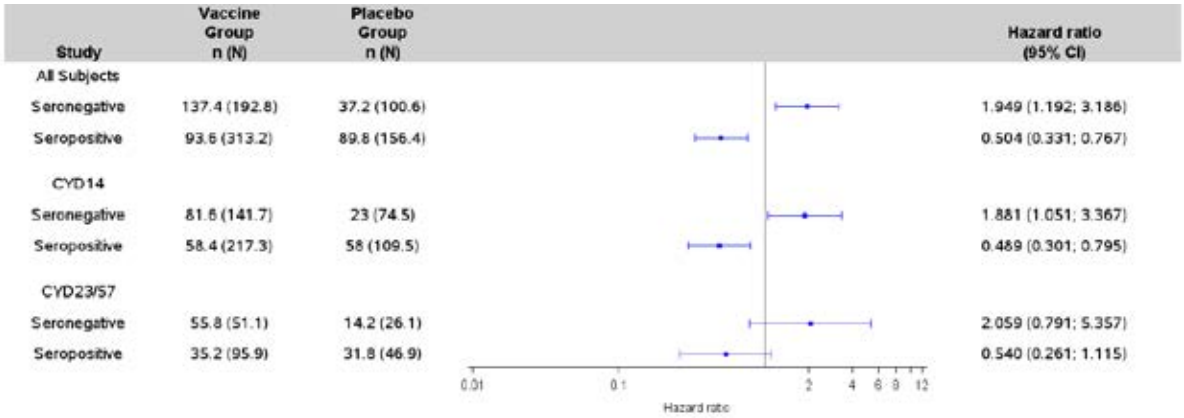
The risk of dengue hospitalization by time period was estimated with the principal and complementary analyses in seronegative subjects < 9 years of age. In the pooled analysis (CYD14 + CYD23/57), the HR/RR was > 1 over the entire study duration including the Active Phase across all methods (except TMLE M0), with statistically significant increased risk observed beyond Y2 of the Hospital Phase for all MI and anti-NS1 methods (HR: 2.709 [95% CI: 1.266, 5.797] by MI M0).

Figure 6: Kaplan-Meier Curve of time to dengue hospitalization from M0 in subjects aged < 9 years at enrolment - serostatus classified by $PRNT_{50}$ at baseline (multiple imputation approach)



The cumulative risk in the CYD Dengue Vaccine Group in seronegative subjects was higher than that in the Placebo Group. There was mostly overlap of the curves for CYD Dengue Vaccine Group over the Placebo Group until around M18, when the curves started diverging. In all of the methods, as the curves reach the end of the follow-up period (approximately beyond M66), there are a small number of subjects at risk

Figure 7: Risk of dengue hospitalization occurring after M0 in subjects aged < 9 years at enrolment - serostatus classified by PRNT at M0



15.3.4.7. Hospitalised dengue by serotype (exploratory objective)

In this study, the risk of hospitalized dengue in seronegative subjects aged > 9 years was > 1 across all methods for serotype 2 and serotype 1.in seronegative subjects aged > 9 years and < 9 years. The HR/RR for serotype 3 was < 1 for all methods except TMLE M0. In the pooled analysis, the HRs/RRs were not statistically significant for any serotype.

15.3.4.8. Severe dengue occurring after M0 or M13 (sensitivity analysis)

The HRs/RRs for the risk of severe dengue in subjects aged ≥ 9 years is summarized in Table 16.

Table 17: Risk of severe dengue (IDMC definition) occurring after M0 or M13 in subjects aged ≥ 9 years at enrolment and classified as seronegative by $PRNT_{50}$ at M0 (measured/imputed)

	Number of Subjects with Cases		Risk of severe dengue		
	Vaccine Group n (N)	Placebo Group n (N)	Hazard Ratio/Relative Risk	95% Confidence Interval	p-value
All studies					
TMLE Month (M)0 onwards*	15.2 (3597.4)	6.8 (2009.7)	1.41	(0.44,4.46)	0.562
MI M0 onwards†	14.8 (375.1)	3.6 (207.2)	2.435	(0.472, 12.559)	0.283
TMLE M13 onwards‡	13.9 (3374.7)	4.2 (1834.6)	2.70	(0.49,14.83)	0.254
MI M13§	13.8 (356.2)	2.6 (189.9)	3.085	(0.477, 19.961)	0.233

In the pooled analysis of studies (CYD14 + CYD15 + CYD57) in seronegative subjects aged ≥ 9 years, the HR/RR were > 1 across both TMLE and MI methods and ranged from 1.41 (TMLE M0) to 3.08 (MI M13). Although the HR/RR was greater than 1, the risk estimated did not reach statistical significance by any method.

Table 18: Risk of severe dengue (IDMC) occurring after M13 in subjects aged ≥ 9 years and classified as seronegative by NS1 (measured at M13)

	Number of Subjects with Cases		Risk of dengue hospitalization		
	Vaccine Group n (N)	Placebo Group n (N)	Hazard Ratio	95% Confidence Interval	p-value
All studies					
Threshold 9 EU/mL	12 (330)	1 (171)	6.251	(0.809, 48.322)	0.079
Threshold 20 EU/mL	16 (393)	4 (205)	2.073	(0.686, 6.262)	0.196
CYD14					
Threshold 9 EU/mL	7 (63)	1 (27)	3.093	(0.366, 26.118)	0.299
Threshold 20 EU/mL	9 (81)	2 (33)	1.922	(0.405, 9.130)	0.411
CYD15					

	Number of Subjects with Cases		Risk of dengue hospitalization		
	Vaccine Group n (N)	Placebo Group n (N)	Hazard Ratio	95% Confidence Interval	p-value
Threshold 9 EU/mL	5 (246)	0 (130)	n/a	n/a	n/a
Threshold 20 EU/mL	7 (287)	2 (155)	1.866	(0.386, 9.020)	0.438
CYD14+CYD15					
Threshold 9 EU/mL	12 (309)	1 (157)	6.134	(0.793, 47.440)	0.082
Threshold 20 EU/mL	16 (368)	4 (188)	2.028	(0.671, 6.134)	0.210
CYD23/57					
Threshold 9 EU/mL	0 (21)	0 (14)	n/a	n/a	n/a
Threshold 20 EU/mL	0 (25)	0 (17)	n/a	n/a	n/a

In subjects ≥ 9 years of age at enrolment and classified as seronegative by anti-NS1 at M13 (Threshold 9), 12 cases of severe dengue were observed in the CYD Dengue Vaccine Group compared to 1 severe case in the Placebo Group (HR: 6.251 [95% CI: 0.809, 48.322], p = 0.079) pooling data across all studies.

In subjects < 9 years at enrolment and classified as seronegative by anti-NS1 (Threshold 9) at M13, a statistically significant imbalance in the number of severe cases between treatment groups was observed. There were 25 severe cases observed in the CYD Dengue Vaccine Group and 4 cases in the Placebo group (HR: 3.433 [95% CI: 1.168, 10.091]).

15.3.4.9. Risk of dengue hospitalization occurring after M0 or M13 in subjects aged ≥ 9 years at enrolment and classified as dengue seropositive by PRNT50 at M0 (measured/imputed) (Exploratory objective)

In contrast to seronegative subjects aged ≥ 9 years, there was statistically significant decreased risk of dengue hospitalization in seropositive subjects from the CYD Dengue Vaccine Group in this age group. In the analysis of pooled studies, all of the estimated HRs/RRs were < 1 and statistically significant. This statistically significant decreased risk was also observed in each individual study and consistent across all methods.

15.3.4.10. Dengue hospitalization in seropositive subjects of any age and < 9 years of age (exploratory objectives)

In the analysis of pooled studies, there was statistically significant decreased risk of dengue hospitalization in the CYD Dengue Vaccine Group for seropositive subjects of any age. The HRs/RRs were consistent across different methods and in individual studies. In seropositive subjects < 9 years of age, a statistically significant decreased risk of hospitalized dengue in the CYD Dengue Vaccine Group was observed in the pooled analysis and in CYD14.

15.3.4.11. Symptomatic VCD in seronegative subjects (secondary objective)

The pooled analysis of CYD14 + CYD15 VE estimate against VCD cases (M0-M25 or M13-M25) in seronegative subjects aged ≥ 9 years ranged from 37% to 45%, depending on the $PRNT_{50}$-based method used, but with a lower bound of the CI below 0, except for the TMLE method. The VE

estimates using anti-NS1 at M13 to define serostatus ranged from 18.0% to 25.3% for pooled studies. The VE was greater (52.4% MI M0) in CYD14 than in CYD15 (34.5% MI M0).

For subjects aged < 9 years, the VE from CYD14 was not statistically significant and ranged from 18.7% to 28% depending upon the $PRNT_{50}$-based method used to assess the baseline serostatus. The VE estimated using anti-NS1 at M13 to define serostatus ranged from 8% to 15%.

15.3.4.12. Symptomatic VCD in seropositive subjects (exploratory objective)

The pooled analysis of CYD14 + CYD15 VE estimate against VCD cases (M0-M25 or M13-M25) in seropositive subjects aged ≥ 9 years was consistent across the methods and showed a statistically significant VE that ranged from 72% - 76% depending upon the $PRNT_{50}$-based method used. The VE estimated using anti-NS1 at M13 to define serostatus was statistically significant and ranged from 76.7% - 78.6%.

The CYD14 VE estimate against VCD cases (M0-M25 or M13-M25) in seropositive subjects aged < 9 years was statistically significant and ranged from 55.6% to 59.5%, depending on the $PRNT_{50}$-based method used.

15.3.5. Conclusion NS1 CSR #2

Several statistical approaches and methods (TMLE targeted minimum loss based estimation method Super-learner, MI, measured anti-NS1 at M13) were used to further describe the safety and efficacy of the CYD dengue vaccine according to baseline dengue serostatus. Estimates of risk of hospitalisation and severe dengue were generally consistent across methods. Descriptions of statistical significance are to be interpreted with caution as adjustments for multiple testing were not performed. The analyses are exploratory in that they had not been initially planned and adequately powered to measure pre-specified outcomes.

Comment: In CSR#2 there remains a misclassification between imputed PRNT M0 seronegativity in the sub-cohort and measured PRNT MO seronegativity in the immunogenicity sub-set. In the immunogenicity subset, among subjects classified as seronegative by multiple imputation, 79.1% were seronegative by measured PRNT50 and 20.9% were seropositive by measured PRNT50.

In seronegative subjects aged ≥ 9 years, there is non-statistically significant increased risk of hospitalized and severe dengue (cumulative to M60 - M72) with modest efficacy against symptomatic dengue up to M25.

In seronegative subjects aged < 9 years, there is increased risk of hospitalized and severe dengue (cumulative to M60 - M72), statistically significant for hospitalized dengue, with no significant efficacy against symptomatic dengue up to M25.

In seronegative subjects 2 to 5 years, statistically significant increased risk is observed against hospitalized dengue. There is an increased risk of hospitalized dengue in subjects aged 6 to 8 and 9 to 11 years (HR/RR > 1 consistent across studies).

In seropositive subjects aged ≥ 9 years, there is statistically significant decreased risk of hospitalized and severe dengue (cumulative to M60 to M72) and statistically significant efficacy against symptomatic dengue up to M25.

In seropositive subjects aged < 9 years, there is decreased risk of hospitalized and severe dengue (cumulative to M60 to M72) and statistically significant efficacy against symptomatic dengue up to M25.

15.3.5.1. Quantitative risk benefit analyses based on NS1 extension clinical study report

The attributable benefit/risk, i.e. the difference in the disease rates in subjects exposed to the vaccine and subjects unexposed to the vaccine, has been calculated from data included in supplemental NS1 analysis. Using the same outcome (hospitalized or severe dengue) to measure

either benefit or risk, the benefit or risk attributable to the vaccine (AR) is defined as the difference in incidence at each time-point, as follows:

AR = incidence in CYD group – incidence in placebo group

AR represents the number of dengue hospitalisations prevented (if AR < 0) or caused (if AR > 0) by the vaccine in a population that has the same dengue incidence as in the clinical studies included in NS1 analysis.

The primary analyses for attributable risk/benefit calculation are based on baseline serostatus by PRNT50, derived from multiple imputation methods and TMLE methods: "Dengue hospitalisation" in subjects aged 9 to 16 years at dose 1 (all studies from M0 for 5 years of follow-up.

In the real world, depending on the setting it may not be feasible to test systematically all individuals before the first dose of vaccination, and therefore one may be interested to assess the benefits and risks of the vaccine when administered to a mixed population of seropositive and seronegative subjects.

In subjects classified as seronegative (that is, with no previous dengue infection detected via PRNT50 test with MI approach), aged 9 to 16 years, it was estimated that during a 5 year follow-up period, about 5 additional hospitalized dengue cases, or 2 additional severe dengue cases per 1,000 vaccinees could occur following vaccination. These results were obtained in a population that had, in non-vaccinated subjects classified as not previously exposed to dengue, a cumulative incidence of 1,09% for hospitalized dengue cases over 5 years, and 0,17% for severe dengue cases over 5 years. In such a population, the estimates from the long-term analysis suggest that the onset of increased risk was mainly during the third year following the first injection.

Figure 8: Attributable risk for hospitalised dengue cases measured in % of exposed seronegative population over 4/5 years

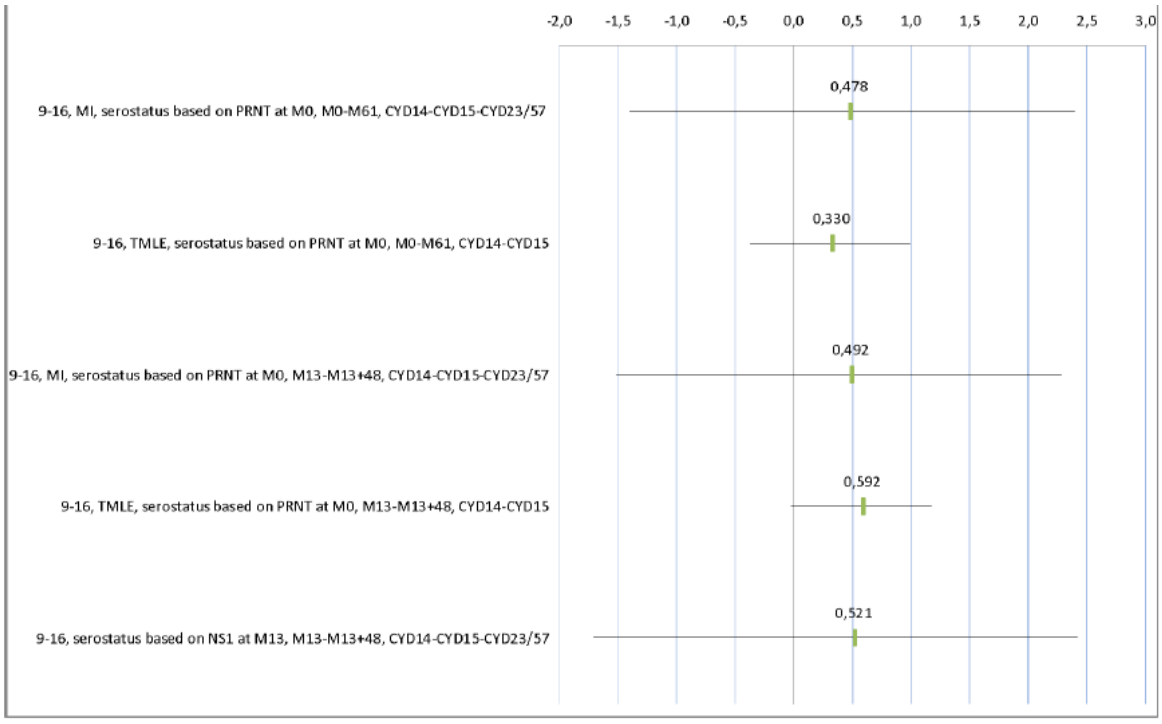
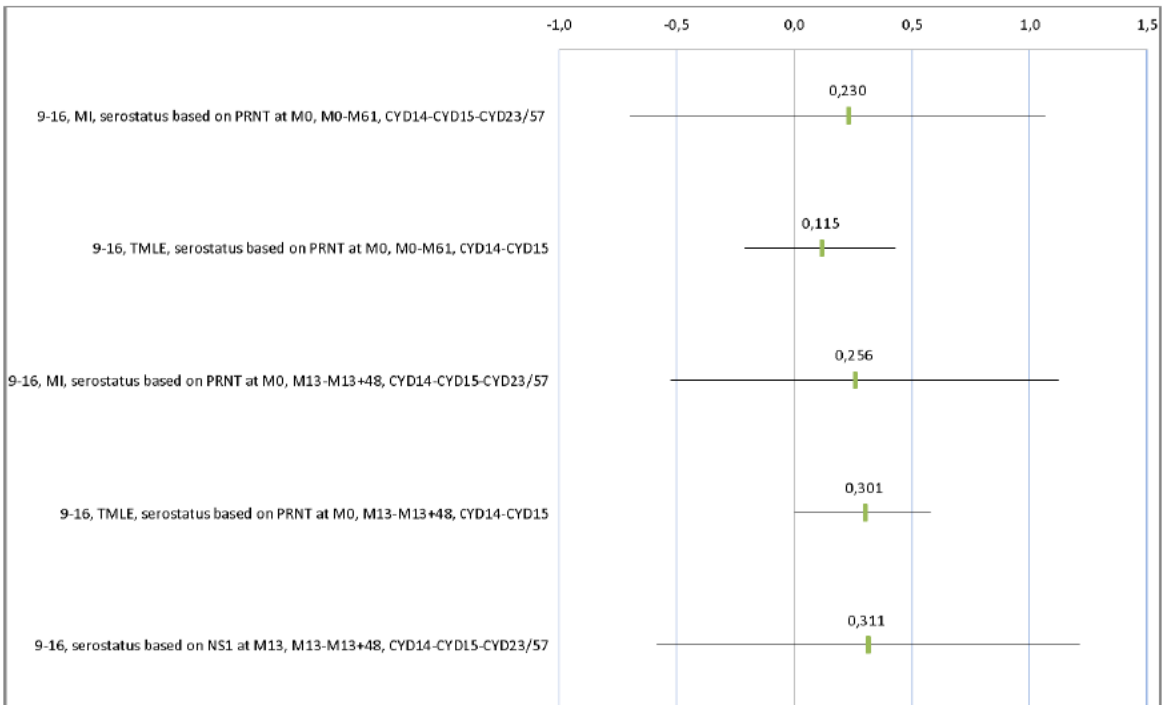


Figure 9: Attributable risk for severe dengue cases measured in % of exposed seronegative population over4/5 years



In year 5 post-dose 1, attributable risks for hospitalized and severe disease in the 9 to 16 years old seronegative population appear to be diminished compared with the preceding 2 years, by both MI and TMLE analyses. In the trial populations, with MI method, this increased risk translates into 5 additional hospitalized and 2 additional severe dengue cases over a 5 year period for every 1000 seronegative subjects vaccinated. In contrast, for every 1000 seropositive subjects vaccinated, 15 hospitalized and 4 severe dengue cases are prevented. In settings with high age specific seropositivity rates (> 80%), and with similar incidence as in the clinical trials, data suggest that vaccination regardless of serostatus has an overall net positive benefit in the population despite risk to the seronegative population. The incidence used for attributable risk/benefit estimates, cumulatively over 5 years, was: for hospitalized cases 1.89% in seropositive subjects and 1.09% in seronegative subjects; and for severe cases 0.48% in seropositive subjects and 0.17% in seronegative subjects. Attributable risk results presented in this report may not be directly applied to any geographical setting, all the more since not only the magnitude of the risk but also the timing (risk period) are driven by the incidence. To address the limitations of attributable risk calculations that are related to the dynamic interactions between incidence and sero-prevalence, a dynamic model has been developed and is presented as an appendix of the current document. Additional limitations are generalisability, with subjects in clinical trials largely healthy volunteers, and data are based on a single symptomatic case and risk of successive dengue infections is unknown.

15.4. Evaluator's assessment and recommendations

This submission proposes changes to Company Core Data sheet for a product indicated for use in individuals living in endemic areas. Dengvaxia is not marketed in Australia. This reviewer considers most SRR proposed changes to PI can be accepted.

The reviewer considers the following proposed paragraph contentious:

> *Vaccination should only be recommended when the potential benefits outweigh the potential risks (for those living in areas with a high dengue seroprevalence or where epidemiological data indicate a high burden of dengue disease) Healthcare professionals*

> *would need to assess the likelihood of prior dengue infection in these individuals before vaccinating. For individuals who have not been previously infected by dengue virus, vaccination should not be recommended. Previous infection by dengue virus can be substantiated through serotesting where available.*

Support for this proposed is provided by a "Quantitative Risk Benefit Analyses based on NS1 extension Clinical Study Report". An alternative currently recommended by WHO is that Dengue vaccine must have previous infection by dengue virus substantiated (through serotesting).

There are significant limitations identified with the sponsor's attributable risk analyses.

WHO undertook a review of CYD dengue vaccine in 2017 and early 2018. WHO acknowledges that in high seroprevalence settings, the vaccine can have significant population level benefit. However, until a full review has been conducted, WHO recommends vaccination only in individuals with a documented past dengue infection, either by a diagnostic test or by a documented medical history of past dengue illness. The reviewer considered that it would be premature to finalise this SRR prior to announcement of the revised WHO position on CYD dengue vaccine.

Revised SAGE recommendations were published on the WHO website on 19 April 2018 and in the weekly epidemiological Record no 23, 8 June 2018.

In June 2018, TGA contacted the sponsor with a request to align the Australian PI for Dengvaxia with the revised SAGE recommendations particularly with respect to the sentence:

> *For countries considering vaccination as part of their dengue control program, a 'pre-vaccination screening strategy' would be the preferred option, in which only dengue-seropositive persons are vaccinated.*

The sponsor proposed an additional sentence, Under Precautions special patient groups:

> *For Australia, a 'pre-vaccination screening strategy' would be the preferred option, in which only individuals previously infected by dengue should be vaccinated.*

The evaluator recommendations on proposed PI are summarised. The sponsor is requested to consider evaluator recommendations for amendment of PI in the summary table and to submit an amended draft PI documents or reasons if there is disagreement.

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