11 November 2021
EMA/754269/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Dengvaxia

Common name: dengue tetravalent vaccine (live, attenuated)

Procedure No. EMEA/H/C/004171/II/0012

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000 An agency of the European Union

Table of contents

List of abbreviations

Ab	antibody
AE	adverse event
AESI	adverse events of special interest
AP	Asia Pacific
AUC-MB	area under the magnitude-breadth curve
CCDS	company core data sheet
CCID	cell culture infectious dose
CI	confidence interval
CSR	clinical study report
CYD	chimera yellow fever dengue
DHF	dengue hemorrhagic fever
Dil	dilution
DS	dengue screen
DSS	dengue shock syndrome
DTaP-IPV/Hib	Diphtheria, Tetanus, Pertussis, Poliomyelitis and Hib vaccine
EC	Ethics Committee
ELISA	enzyme linked immunosorbent assay
EMA	European Medicines Agency
FAS	full analysis set
FASE	full analysis set for efficacy
FASI	full analysis set for immunogenicity
FDA	Food and Drug Administration
FHCRC	Fred Hutchinson Cancer Research Center
FV	flavivirus
GCP	good clinical practice
GMT	geometric mean of titers
GMTR	geometric mean of titer ratio
HVCD	Hospitalized virologically-confirmed dengue
ICH	International Conference on Harmonisation
IDMC	Independent Data Monitoring Committee
IFNγ	interferon gamma
Ig	immunoglobulin

IL	interleukin
IM	intramuscular
IVRS	interactive voice response system
JE	Japanese encephalitis
LatAm	Latin America
LLOQ	lower limit of quantitation
LTFU	long-term follow-up
MMR	measles, mumps and rubella
NC	not computed
NI	non-inferiority
PCV	pneumococcal conjugate vaccine
PD	post-dose
PLA	placebo
PPAS	per-protocol analysis set
PRNT	plaque reduction neutralization test
RCDC	reverse cumulative distribution curve
RR	relative risk
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SC	subcutaneous
SEP	Surveillance Expansion Phase
SVCD	severe virologically-confirmed dengue
ULOQ	upper limit of quantitation
VCD	virologically confirmed dengue
VE	vaccine efficacy
WHO	World Health Organization
WT	wild-type
YF	yellow fever

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, on 25 August 2020 Sanofi Pasteur submitted an application for a variation to the European Medicines Agency.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include paediatric population from 6 years of age for Dengvaxia; as a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC and sections 1, 2 and 4 of the Package Leaflet are updated. Furthermore, the MAH takes the opportunity to add an instruction for the installation of the needle in the SmPC and the Package Leaflet of the single-dose presentation.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet.

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0065/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP EMEA-001545-PIP01-13-M02 was completed.
The PDCO issued an opinion on compliance for the PIP EMA/PDCO/172848/2020.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH did not seek Scientific Advice at the CHMP.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Christophe Focke

Timetable	Actual dates
Submission date	25 August 2020
Start of procedure:	12 September 2020
CHMP Rapporteur Assessment Report	9 November 2020
CHMP members comments	30 November 2021
Updated CHMP Rapporteur(s) (Joint) Assessment Report	3 December 2020
Request for supplementary information (RSI)	10 December 2020
CHMP Rapporteur Assessment Report	27 April 2021
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	12 May 2021
Request for supplementary information (RSI)	20 May 2021
CHMP Rapporteur Assessment Report	27 October 2021
CHMP members comments	n/a
Updated CHMP Rapporteur Assessment Report	05 November 2021
Opinion	11 November 2021

2. Scientific discussion

2.1. Introduction

In the EU, at the time of this application, Dengvaxia was indicated for the *prevention of dengue disease caused by dengue virus serotypes 1, 2, 3, and 4 in individuals 9 to 45 years of age with prior dengue virus infection and living in endemic areas*. The current vaccination schedule consists of 3 injections 6-month apart.

At the time of the granting of the initial Marketing Authorisation, the MAH committed to assess the benefit/risk of Dengvaxia in younger populations below 9 years of age once the 2 pivotal efficacy studies, CYD14 and CYD15, were completed. As the final results of CYD14 and CYD15 studies became available, the MAH performed analyses of new and existing clinical data. Based on the results, the MAH proposed an extension of the age specified in the indications to include children 6 to 8 years of age dengue seropositive at baseline.

Problem statement

Disease or condition

Dengue is an acute, systemic viral infection caused by a virus that is transmitted primarily by the Aedes aegypti mosquito bites. The infection may be asymptomatic, cause flu-like illness, and can develop into a potentially lethal complication called severe dengue (including dengue hemorrhagic fever [DHF]/dengue shock syndrome [DSS]).

There are 4 types of closely related but antigenically distinct dengue virus serotypes (1, 2, 3, and 4). Primary dengue virus infection is thought to provide lifelong protection against the infecting serotype and transient cross-protection against heterologous serotypes. Dengue haemorrhagic fever and dengue

shock syndrome occur mostly in individuals during secondary dengue virus infection with a different serotype.

Claimed therapeutic indication

With this variation, the MAH applied for an extension of the approved indication (SmPC section 4.1) to include children 6 to 8 years of age dengue seropositive at baseline:

*Dengvaxia is indicated for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in individuals **6** to 45 years of age with prior dengue virus infection and living in endemic areas.*

Epidemiology and risk factors

Dengue is the most common mosquito-borne viral disease in humans, spreading globally during the past 30 years as a result of changes in human ecology. The rapidly expanding global footprint of dengue inflicts a significant public health, economic and social burden on the populations of endemic areas. Half of the world's population is now considered at risk of infection by the dengue viruses. Worldwide, an estimated 390 million dengue infections occur every year, of which around 100 million are associated with clinical manifestation of dengue. Around 500.000 hospitalizations are reported each year, and around 20.000 cases result in death.

Geographical distribution

Dengue disease is a major public health concern in more than 128 countries, with the four dengue virus serotypes found in tropical and sub-tropical regions, including some European territories.

The terms 'endemicity' and 'hyperendemicity[1]' are used to indicate the simultaneous circulation of one or several Dengue virus serotypes, respectively. Dengue epidemiology varies across regions and seasons. An endemic region is defined as a region where cases are present over the majority of time during the year. This means that transmission is constantly ongoing. In contrast, an epidemic region is a region where cases are only present during a short period of time. Yearly epidemics can happen, or an epidemic can happen over several years.

Dengue is endemic in Asia, the Pacific area, Africa, and Latin America (including the Caribbean). In 2017, more than 500.000 dengue cases were reported to the WHO South-East Asia office and in 2019 more than 1 million cases were reported to the WHO Western Pacific region main countries for dengue (i.e., Australia, Cambodia, Lao Popular Democratic Republic, Malaysia, Philippines, Singapore and Viet Nam).

A decrease of 75% in number of dengue cases was reported across the Americas in 2017 and 2018, compared to 2016. However, the incidence of disease increased again in 2019 with a total of more than 3 million cases reported for the WHO Americas region.

After decades of absence in the United States of America (US), dengue has recently emerged with cases which were locally acquired.

Sustained transmission of dengue fever does not naturally occur in continental Europe, though sporadic autochthonous dengue cases had been reported in Croatia in 2010 and in France in 2010, 2013, 2014, and 2015, even if more limited. Dengue, however, is endemic in the overseas territories of some European countries such as France (French Guiana, Martinique and Guadeloupe).

In 2020, dengue continues to affect several countries, with reports of increases in the numbers of cases in Bangladesh, Brazil, Cook Islands, Ecuador, India, Indonesia, Maldives, Mauritania, Mayotte (Fr),

[1] Trop. Med. Infect. Dis. 2020, 5, 156; doi:10.3390/tropicalmed5040156

Nepal, Singapore, Sri Lanka, Sudan, Thailand, Timor-Leste and Yemen.

While geographical expansion of dengue and its vector are evident, the true burden of symptomatic dengue disease is underestimated. The true numbers are probably far worse, since significant underreporting and misclassification of dengue cases have been documented. Constraints inherent to public health surveillance systems and challenges specific to dengue do not allow dengue cases to be fully captured by public health surveillance systems.

Age and serotype distribution

In endemic areas, the entire population is at risk of dengue infection. The disease affects all age groups. The age distribution of infected individuals varies between countries and no clear pattern of populations at risk has been identified. For example, incidence rates were highest in adults in Mexico, Malaysia, and in the French Caribbean, highest in adolescents in Brazil and Thailand, and highest in children in the Philippines and Colombia. Additionally, the population at highest risk can shift over time, as was observed in Colombia and Thailand over the last decade.

Dengue epidemiology is dynamic in terms of serotype circulation. The seroprevalence of each serotype fluctuates over time. The four dengue virus serotypes are genetically diverse and share limited identity (around 60-75%) at the aminoacid level. Genetic variations between serotypes and clades may be important determinants of differential viral fitness, virulence and epidemic potential.

Risk factors for severe dengue

Epidemiologic studies have identified young age, female sex, high body-mass index, virus strain, and genetic variants of the human major-histocompatibility-complex class I–related sequence B and phospholipase C epsilon 1 genes as risk factors for severe dengue.

Young children in particular may be less able than adults to compensate for capillary leakage and are consequently at greater risk of dengue shock.

Chronic disease (bronchial asthma, sickle cell anaemia and diabetes mellitus) and ethnicity may represent additional individual risk factors that determine the severity of disease.

Secondary infection as risk factor for severe dengue

Primary dengue virus infection is thought to provide lifelong protection against the infecting serotype and transient cross-protection against heterologous serotypes. Dengue haemorrhagic fever and dengue shock syndrome occur mostly in individuals during secondary dengue virus infection with a different serotype. Increased risk in secondary infection is thought to be linked to antibody-dependent enhancement of virus infection in Fc receptor–bearing cells and the generation of a large infected cell mass in vivo The antibody-mediated enhancement of dengue seems to be related with the presence of suboptimal neutralizing heterotypic antibodies (that accelerate the rate of internalization of the virus and infection of host cells), and may also be related to the presence of memory T cells with low affinity for the present infecting virus but high affinity for previous infecting serotype(s).

Clinical presentation and diagnosis

Dengue disease has a wide and unpredictable range of clinical presentations, from asymptomatic to severe diseases. According to CDC, an estimated 1 in 4 dengue virus infections are symptomatic. Symptomatic dengue virus infection most commonly presents as a mild to moderate, nonspecific, acute febrile illness. Approximately 1 in 20 patients with dengue virus disease progress to develop severe, life-threatening disease called severe dengue. Severe dengue is a potentially fatal complication, due to plasma leaking, fluid accumulation, respiratory distress, severe bleeding, or organ impairment. Dengue

shock syndrome (DSS) is the most severe form of dengue disease and results from hypovolaemia caused by vascular leakage. Early clinical findings are nonspecific but require a high index of suspicion because recognizing early signs of shock and promptly initiating intensive supportive therapy can reduce risk of death among patients with severe dengue to <0.5%.

Diagnostic methods to confirm dengue virus infection may involve detection of viable virus, viral nucleic acid, peripherally circulating viral antigens or host antibodies, or a combination of these techniques. Depending on the time of patient presentation, the application of different diagnostic methods may be more or less appropriate. After the onset of illness, dengue virus can be detected in serum, plasma, circulating blood cells and other tissues for four to five days. Dengue infections may therefore be diagnosed by detection of viral RNA RT-PCR, or by detection of viral antigens, such as the NS1 antigen (by rapid tests). After day 5, dengue viruses and antigens disappear from the blood and specific antibodies appear, making serology the method of choice for diagnosis. Detection of IgM by ELISA or of neutralizing antibodies by PRNT could, among others, be used. It should however be mentioned that people infected with or vaccinated against other flaviviruses (such as Zika, West Nile, yellow fever, and Japanese encephalitis viruses) may produce cross-reactive flavivirus antibodies, yielding false-positive serologic dengue diagnostic test results (WHO, CDC, Verhagen 2014).

Management and prevention

There is no specific treatment for dengue disease. The management of dengue disease is supportive, with rest, control of fever and pain with antipyretics/analgesics, and adequate fluid intake. Supportive intensive care and fluid management are the mainstays of therapy for severe disease.

Up to the end of 2015, the only available prevention of dengue by vector control has proven to be of limited success, very difficult to sustain and costly. Vaccination provides a viable and practical alternative in disease control measures. The only vaccine currently on the market is Dengvaxia.

Since the first marketing authorization obtained in Mexico on 8 December 2015, Dengvaxia has been licensed in 22 countries in total. However, due to a suspension for the license in the Philippines and the non-renewal in Malaysia, at the time of this application the vaccine was registered by 21 regulatory authorities across the world.

Based on EMA's CHMP recommendation, the European Commission has granted the marketing authorization in Europe on 12 December 2018. The prequalification by the World Health Organization (WHO) was granted on 25 March 2020.

Unmet medical need

Dengvaxia is indicated for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in individuals 9 to 45 years of age with prior dengue virus infection and living in endemic areas. The MAH proposed to extend the indication to include children 6-8 years of age, as suggested by health authorities.

Similarly to adults, children experiencing a secondary dengue infection have a much higher risk of developing severe dengue. Children are however at a higher risk of severe dengue. National surveillance data from Asian countries show that infants under 1 year of age and children aged 4–9 years have consistently been at the highest risk for severe dengue disease (Guzman 2002, Verhagen 2014), underlying the need to vaccinate children below 9 yoa.

2.2. About the product

CYD dengue vaccine is a tetravalent, recombinant, live attenuated viral vaccine. The viruses in the vaccine consist of the replicative engine of the attenuated yellow fever vaccine virus 17D (coding for the non-structural proteins and capsid), along with the genes coding for the pre-membrane and envelope proteins of each of the 4 wild-type dengue serotypes.

CYD dengue vaccine consists of a sterile, freeze-dried powder formulation that is reconstituted with a sodium chloride solution (0.4% for the single-dose presentation, 0.9% for the multi-dose presentation) before injection and does not contain any adjuvant or preservative. Each dose contains 4.5-6.0 log-10 Cell-Culture Infectious Dose 50% (CCID50) per serotype (as per CCDS and EU Product Information).

After reconstitution, one dose (0.5 mL) is to be administered by the subcutaneous route.

Compliance with CHMP guidance

All the clinical studies providing some new data used to update the integrated analyses and support the present variation were included in the Dengvaxia RMP.

This extension of age indication in younger populations below 9 years of age has been considered since the time of licensure, when it was agreed with several regulatory authorities that the benefit/risk would have to be assessed below 9 years of age once the 2 pivotal efficacy studies had been completed.

General comments on compliance with GCP guidelines

All clinical studies evaluating the CYD dengue vaccine comply with the guidelines in force during the CDP, such as: the Quality Standards of the International Conference on Harmonization (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.

Non-clinical aspects

No new clinical data have been submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

Introduction

At the time of the initial MAA, the MAH aimed at an indication irrespective of age and serostatus (i.e. whether a person has had a previous DENV infection before vaccination), based on the data of the pivotal trials in endemic regions.

Data were presented irrespective of serostatus, and analyses stratified by age were performed. At that time, it was observed that efficacy (over the initial two years) increased with age, and was inconclusive in the youngest 2-5 years of age (YOA) category. Importantly, a harmful effect of CYD dengue vaccine (higher risk of hospitalized dengue in children who received CYD dengue vaccine as compared to the controls) was detected in the 2-5 years group starting from Year 3 (the first year of long-term follow-up [LTFU]). Cumulatively, this translated to an about 20% excess risk of hospitalized dengue over 5 years (the period for which data were available at that time) in CYD vaccinated 2-5 years old children vs controls. This finding was not statistically significant, but it was considered plausible that it actually

reflects the greater proportion of dengue naïve subjects in the youngest group, in whom sensitization to severe dengue may occur through mechanisms such as antibody disease enhancement (ADE).

In additional exploratory pooled stratified analyses in the immunogenicity subset, CYD dengue vaccine was found poorly effective in subjects who are not dengue immune (i.e. seronegative subjects) at baseline. Starting from Years 3, the pattern observed in dengue seronegatives was very similar to the pattern found in the youngest children. Although the independent effect of age and baseline serostatus on vaccine efficacy/safety could not be determined robustly given the small sample size of the immunogenicity subset, data tended to suggest that the increased risk of hospitalized dengue associated to CYD dengue vaccine during Year 3 was concentrated in dengue non-immune subjects, whatever the age. In contrast to dengue naïve subjects, data consistently suggested high VE (approx. 80%) in individuals who have had a past dengue exposure (i.e. seropositive subjects), whatever their age, and no safety issue on the long term. It was concluded that in dengue naïve subjects, CYD dengue vaccine is a weak primer, which induces immunity of poor quality, rapidly waning, and potentially sensitizing to severe dengue. In contrast, for individuals who have experienced at least one dengue virus infection, CYD dengue vaccine constitutes a booster of pre-existing immunity which protects against infections with new heterologous serotypes.

The MAH subsequently performed the post hoc NS1 analyses whereby testing on M13 samples were used as a surrogate of past dengue exposure. This allowed assessing efficacy and safety according to serostatus in a larger population. These analyses confirmed a negative benefit-risk for seronegative individuals vaccinated with CYD dengue vaccine, whatever their age.

In this context, at the time of the initial MAA, the MAH proposed an age-based approach for the sought indication, considering that with an age range of 9-45 years, a positive benefit-risk would be obtained overall in endemic areas (as the proportion of seronegatives would be sufficiently low). Based on post-hoc modelling approaches (kernel smoothing curve) showing VE against symptomatic VCD cases and relative risk against hospitalized VCD cases in studies CYD14, CYD15 and CYD23/57 as a function of age, the MAH considered that significant efficacy and the absence of an imbalance in hospitalized VCD and hospitalized severe VCD were observed as off 9 years. The proposal of the MAH to restrict the indication to children ≥9 YOA whatever the baseline serostatus of the individual has not been considered acceptable given that the benefit/risk in the naïve subpopulation remained negative, whatever the age. This lead to the current indication, restricted to persons with prior dengue virus infection. Despite that restriction, the MAH preferred to keep the lower age limit of 9 years in the indication, because of the lack of understanding of the independent effect of age.

During the initial MAA, it was already noted that earlier Phase 1 and 2, and large-scale Phase 3 efficacy studies with the CYD dengue vaccine suggested that the vaccine has satisfactory immunogenicity and safety profiles in dengue seropositive participants aged 6 to 8 years. The Phase 3 efficacy studies also provided preliminary evidence that, among dengue seropositive participants, the vaccine could be efficacious in preventing virologically-confirmed dengue disease in subjects aged 6 to 8 years.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH.

Overview of data supporting the present extension of indication

To support this extension of the age specified in the indications to include children 6 to 8 years of age, the MAH presented data from new integrated analyses carried out with the existing overall clinical dataset implemented with the new available clinical data. The integrated analyses of safety, immunogenicity,

and efficacy presented in the initial registration have been updated with new available data:

1) Final results (long-term follow-up data) of the 2 pivotal efficacy studies CYD14 and CYD15. Data of 5 years follow-up after the last injection are now available.

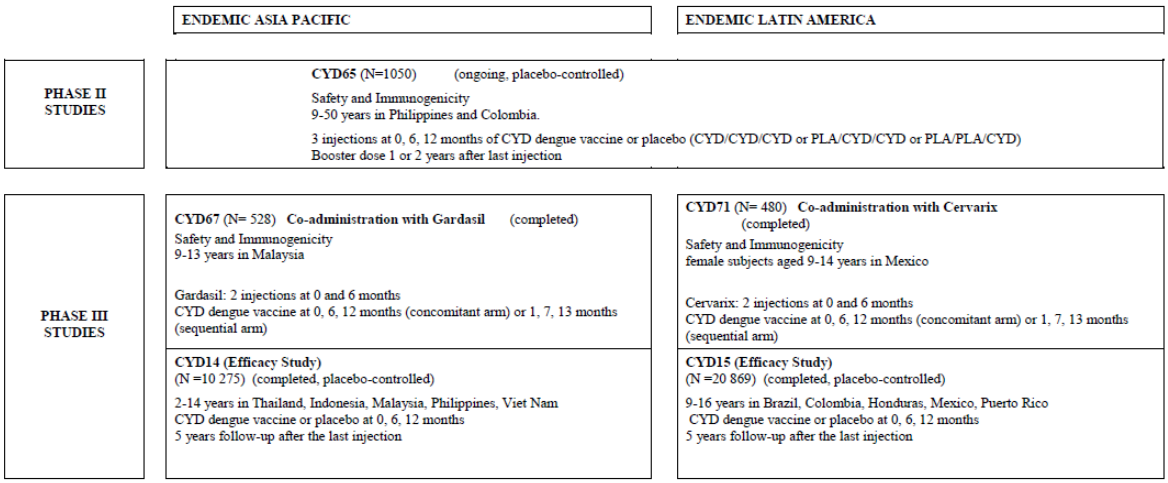
2) Interim results of CYD65, a Phase 2 study that assesses reduced primary vaccination schedules (2-dose and 1-dose schedules instead of 3-dose schedule) and booster dose in seropositive subjects 9 to 50 years of age in the Philippines and Colombia. Results up to 1 year after the primary vaccination schedule and 28 days after the booster injection (given at Year 1) are available. The study is still ongoing.

3) Results of 2 co-administration studies (CYD67, and CYD71). These Phase 3b studies assessed the feasibility of co-administration of 2 human papilloma virus vaccines (tetravalent and bivalent) with the CYD dengue vaccine in terms of immunogenicity and safety in subjects aged 9 to 13-14 years.

These last 3 studies (CYD65, CYD67, and CYD71), which included subjects aged above 9 years, allowed to increase the clinical database and were used for the comparison of results in subjects aged 6 to 8 years with those in subjects aged 9 years and above.

The main features of the new studies included in the integrated analyses are provided below.

Figure 1: Overview of new studies included in the integrated analyses



In addition, the extension of the age indication down to children 6 to 8 years of age is supported by the NS1 Supplemental Analyses.

The presentation of immunogenicity and efficacy data in the new target population (6 to 8 years) is accompanied by an outline of the data in subjects 9 to 17 years and 2 to 5 years, presented as benchmark and to update results from the prior submission. The presented results focus on baseline seropositive subjects in line with the approved recommendations.

Pharmacokinetics

Not applicable.

Pharmacodynamics

Refer to the immunogenicity section.

Efficacy data

In order to support the extension of the indication to include children 6 to 8 years of age, the integrated analyses of efficacy presented in the initial registration have been updated with the final results (long-term follow-up data) of the 2 pivotal efficacy studies CYD14 and CYD15. Data of 5 years follow-up after the last injection have also become available.

Vaccine efficacy (VE) against symptomatic virologically-confirmed dengue (VCD) cases is presented in seropositive children 6 to 8 years of age, during the Active Phase, and during the surveillance expansion phase (SEP). Seropositive subjects aged 9 to 16 years are also presented as a benchmark, along with seropositive subjects aged 2 to 5 years in order to provide some perspective on VE in the younger age group. Finally, VE is also presented in seropositive subjects aged 6 to 16 years to provide a comprehensive overview of efficacy.

Table 1: Number of seropositive subjects considered for the assessment of efficacy (Immunogenicity Subset) in the CYD dengue vaccine and Placebo groups

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

Source: modified from 5.3.5.3 Integrated Efficacy Analysis Report, Table 3.6.6.4, Table 3.6.8.39, and Table 3.6.6.3 (see "Integrated Summary of Efficacy [ISE] - Tables and Figures" submitted in eCTD sequence 0029)

In addition, the extension of indications to children 6 to 8 years of age is supported by the results of the NS1 Supplemental Analyses.

The actual numbers of subjects aged 6 to 8 years considered for the assessment of efficacy of the vaccine, supporting the extension of age indication, are presented in Table 1. The number of subjects in the age groups 2 to 5 years and 9 to 17 years is also presented when the comparison to these age groups was used in the analyses.

Dengue seropositivity was defined as a neutralizing Ab level ≥ 10 1/dil against at least one dengue serotype before the first injection, measured by PRNT50.

The efficacy of the CYD dengue vaccine was also assessed in 236 baseline dengue seropositive subjects aged 6 to 8 years (169 subjects in CYD14 and 67 subjects in CYD23) who received the CYD dengue vaccine and 126 baseline dengue seropositive subjects aged 6 to 8 years (88 subjects in CYD14 and 38 subjects in CYD23) who received the placebo.

In addition, the NS1 Supplemental Analyses was used to impute the dengue serostatus at baseline in order to increase the precision of the vaccine efficacy and long-term safety assessments.

The CHMP noted that, to support this extension indication to younger age groups, the MAH presented integrated analyses of efficacy updated with the final results of CYD14 and CYD15 for which data of 5 years follow-up after the last dose are now available. Integrated analyses of efficacy include subjects aged 2 to 16 years from the Phase 3 efficacy trials (CYD14, 2-14 years and CYD15, 9-16 years) and from the Phase 2b PoC (CYD23, 4-11 years) trial. The MAH presented efficacy data in the new target population of the claimed indication (children 6 to 8 years), which are mainly data from CYD14 (and

limited data from CYD23). The MAH presented efficacy data in children 9-16 years (CYD14 and CYD15) and 2-5 years (CYD14 mainly), as a benchmark and to update results from the prior submission. Data in the overall population 6-16 years (i.e. all available efficacy data supporting the new indication) are also presented.

As the indication is limited to subjects with prior dengue virus infection, the efficacy analyses focused on seropositive subjects. Therefore, these analyses are limited to subjects for whom baseline serostatus data are available (Immunogenicity Subset).

Dengue seropositivity was defined as a neutralizing Ab level ≥ 10 1/dil against at least one dengue serotype before the first injection, measured by PRNT50. The MAH approach was considered acceptable given the already low number of subjects in the subset, and considering that biases (if any) are not expected to lead to overestimation of VE. In contrast, there could be non-differential misclassification, leading to underestimation of VE (dilution). In addition, the NS1 Supplemental analyses considered PRNT90.

The NS1 Supplemental Analyses performed in the same studies are also presented as supportive data, as this allowed an assessment on a larger number of subjects.

A similar approach (analyses in the Immunogenicity Subset, supported by NS1 Supplemental Analyses) was used to assess the effect of Dengvaxia over the longer term, during the Hospital Phase and over the entire study period (effect on dengue, hospitalised dengue and severe dengue). This was considered as safety analysis by the MAH (instead of efficacy). This distinction between efficacy and safety data is considered artificial, but reflects the initial design of the studies (see below). Long-term safety/efficacy data analyses are presented in the safety but discussed together with the efficacy data in the efficacy section.

Design of the (three) Efficacy Studies

The CYD dengue vaccine development program included 2 pivotal large-scale randomised placebo-controlled Phase III efficacy studies: CYD14 and CYD15, conducted in endemic countries.

CYD14 randomized 10,275 children 2 to 14 years (6851 CYD dengue vaccine vs. 3424 placebo) in Indonesia, Malaysia, Thailand, the Philippines, Viet Nam.

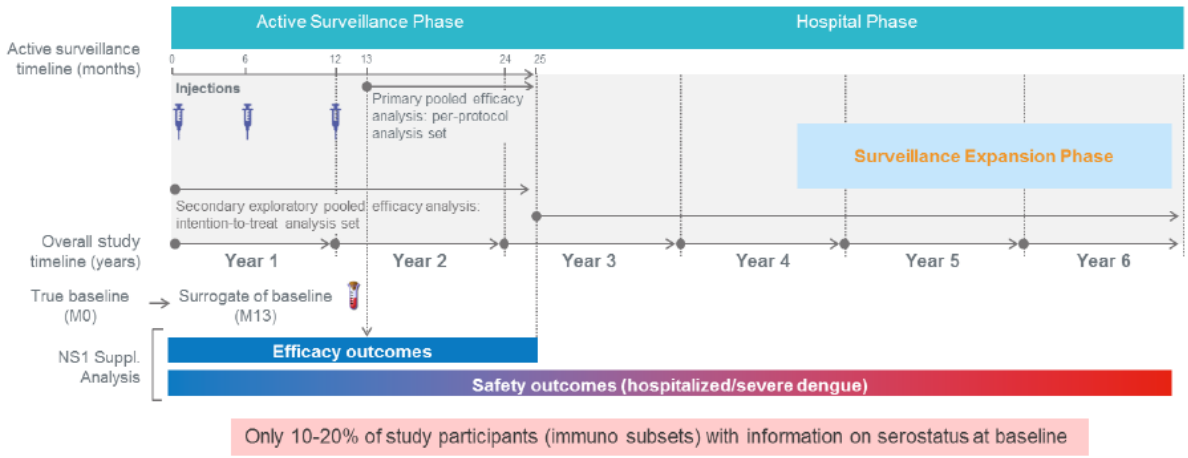
CYD15 randomized N=20,869: children 9 to 16 years (13,920 CYD dengue vaccine vs 6949 placebo) in Brazil, Colombia, Honduras, Mexico, Puerto Rico.

Both studies lasted approximately 6 years including an active surveillance phase (i.e. from M0 to M25) to mainly assess vaccine efficacy (VE) and a hospital phase (i.e. M25 to M72), for detection of hospitalized cases with follow-up for an additional 4 years (i.e. 'long term follow-up' [LTFU]).

An active surveillance system (i.e. 'surveillance expansion phase' [SEP]) was reinstituted in both studies after the detection of a safety signal in study CYD14 to better monitor VE and safety, covering approximately the last 2 years of the planned follow-up period.

The overall design and important timelines of CYD14 and CYD15 are presented Figure 2.

Figure 2: Outline of CYD14 and CYD15 Study Design and Timelines



The third study, Study CYD23 was a Phase IIb efficacy study conducted in Thailand among children 4 to 11 years with a similar study design. Active surveillance (Active Phase) was performed during the first 2 years of the study. Subjects from study CYD23 were then followed in a hospital surveillance in CYD57 for 4 years. However, no SEP was instituted as this study was finalized at the time the safety signal in study CYD14 was detected. As a Proof of Concept (PoC) study, the sample size in CYD23 was smaller than in CYD14 and CYD15. In addition, there were slight differences in dengue cases definitions and laboratory methods and testing algorithm.

The primary objective of the efficacy studies was to assess the efficacy of the CYD dengue vaccine after 3 injections administered 6 months apart in preventing the occurrence of symptomatic VCD cases due to any of the 4 serotypes. For the primary endpoint, the incidence of symptomatic VCD cases occurring > 28 days after the third injection was compared to the Control Group.

Briefly, the 2 Phase III efficacy studies (CYD14 and CYD15) were essentially identical in terms of study design, vaccine formulation and schedule, objectives, definition of endpoints, power and targeted VE assumptions. The CYD23 differed from Phase III efficacy studies, as it was a PoC study designed to assess preliminary proof of efficacy, in a restricted geographic coverage (mono-centric mono-country study), and with a different algorithm used for defining a VCD case.

In these three efficacy studies, dengue baseline serostatus was assessed in an Immunogenicity Subset corresponding to approximately 7.5% (N=300), 10% (N=2000), and 20% (N=2000) of study participants in CYD23, CYD15, and CYD14, respectively.

The CHMP noted that the studies were similar in terms of study design. CYD14 and CYD15 used the same endpoints definitions. The CYD23 used a slightly different dengue cases definition, laboratory methods and testing algorithm (see below).

Objectives

The main objectives and endpoints presented in the Immunogenicity Subset considered for the assessments are described below. They are analogous to those considered for the efficacy assessments in the NS1 Supplemental Analyses. The statistical criteria for assessment of VE on the Immunogenicity Subset were consistent with criteria previously used in the Integrated Efficacy Analysis Report.

1) Efficacy in baseline dengue seropositive subjects aged 9 to 16 years, 6 to 8 years, and 6 to 16 years during the Active Phase

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

2) Efficacy in baseline dengue seropositive subjects aged 9 to 16 years, 6 to 8 years, and 6 to 16 years during the Surveillance Expansion Phase (SEP)

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

The CHMP noted that the main objectives of the efficacy analyses performed to support this extension of indication are similar in the Immunogenicity Subset and the NS1 Supplemental analyses and consistent with the previous Integrated Efficacy Analyses. Efficacy was assessed in dengue seropositive subjects aged 2-5 years (not mentioned in the objectives described by the MAH although the analyses were done), 6 to 8 years and 9 to 16 years, and 6 to 16 years during the whole Active Phase (M0-M25) and the Surveillance Expansion Phase (SEP) from the time of consent until the end of the study.

Efficacy was assessed in preventing the occurrence of VCD due to any serotype and to each serotype. Efficacy in preventing HDCV and SVCD (as per IDMC definition) was also assessed.

Endpoints

Main endpoints and definitions relevant to the above-described objectives were as follows:

Symptomatic VCD cases due to each or any serotype occurring:

- During the Active Phase, after at least one injection; i.e, occurring after the first injection until the end of the Active Phase.
- During the SEP; i.e. from date of subject reconsent to enter in the SEP until the end of the study, after at least one injection (only for CYD14 and CYD15, since no SEP was implemented in CYD23/57).

SVCD (IDMC) and HVCD cases due to any serotype occurring:

- During the Active Phase.
- During the SEP (only for CYD14 and CYD15).

NS1 Supplemental Analyses

In the three efficacy studies, dengue baseline serostatus was assessed in an Immunogenicity Subset corresponding to approximately 7.5%, 10%, and 20% of study participants in CYD23, CYD15, and CYD14, respectively. Baseline serostatus of the other participants could not be determined as no samples had been collected at baseline (M0), limiting the precision of efficacy estimates.

In order to improve precision of VE estimates by increasing the size of the population assessed, Sanofi Pasteur leveraged a dengue anti-nonstructural protein 1 (NS1) IgG enzyme-linked immunosorbent assay to test samples collected from each participant at Month 13 (M13; i.e. 1 month after the third vaccine dose). Blood samples from M13 were available from almost all individuals as per study design; however, they could not be analyzed with the traditional PRNT assay used to assess serostatus at baseline since it is largely affected by the vaccine and could not distinguish between vaccination and prior dengue infection.

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

The NS1 Supplemental Analyses were based on a case-cohort design to obtain efficacy and risk estimates according to dengue serostatus.

Definition of the Case-Cohort

The case-cohort design in the NS1 Supplemental Study, based on the approach introduced by Prentice (Prentice RL. A case-cohort design for epidemiologic cohort studies and disease prevention trials. Biometrika. 1986;73(1):1-11.), where, a random sample of subjects, referred to as the sub-cohort, was first chosen from the entire study population. Subjects with the event of interest but not selected in the sub-cohort were then included in the case-cohort analysis.

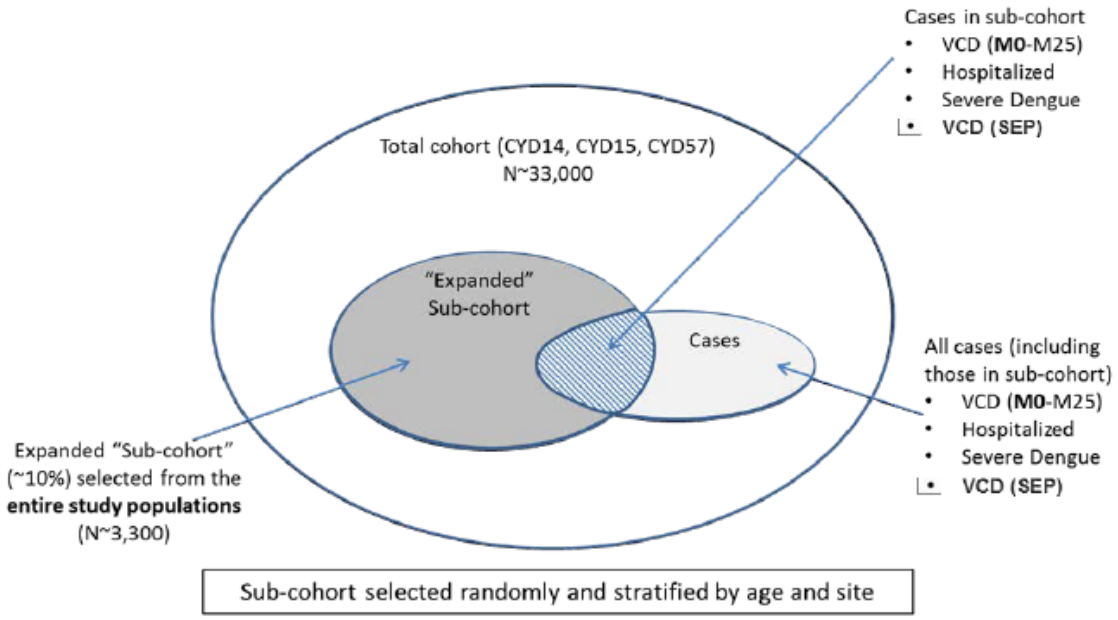
The sub-cohort included a random selection of approximately 10% of the entire study cohorts of CYD14, CYD15, and CYD23/57 after stratifying for age and trial site, ie approximately 3500 subjects.

The cases, corresponding to all events of interest (whether included or not in the sub-cohort), were all symptomatic VCD which occurred in CYD14, CYD15, and CYD23/57 during the Active Phase or in CYD14 and CYD15 during the SEP, and all HVCD and SVCD until the end of each study, depending on the analysis.

Subjects from CYD23/57 were included in the sub-cohort. However, VCD cases from that study were not included in efficacy assessments in the NS1 Supplemental Analyses as consent from these subjects could not be obtained.

The case-cohort included individuals from the sub-cohort (with or without VCD cases) plus remaining individuals with VCD events. The case-cohort design is represented in Figure 3.

Figure 3: Diagrammatic representation of case-cohort design



Source: Modified from 5.3.5.4 NS1 Extended CSR, Figure 3.1

The CHMP noted that, given that the majority of study participants had no pre-vaccination blood sample, the MAH developed an approach to indirectly assess baseline serostatus by testing M13 samples (i.e. 1 month after the third vaccine dose), which were taken in all subjects. PRNT assay could not be used as it is not able to distinguish immunity induced by vaccination and prior dengue infection. Therefore, the MAH developed a dengue anti-nonstructural protein 1 (NS1) IgG enzyme-linked immunosorbent assay (ELISA). This NS1 assay aims at differentiating anti-NS1 antibodies induced by wild-type dengue infection from those induced by vaccination (since the CYD dengue vaccine contains genes encoding NS1 from the yellow fever 17D vaccine virus rather than from dengue virus).

This led to the NS1 Supplemental Analyses, which confirmed the safety issue in seronegatives (see previous assessments). The NS1 Supplemental Analyses aimed at obtaining efficacy and relative risk estimates according to dengue serostatus in the efficacy trials.

A case-cohort design was used. A sample of subjects, referred to as the sub-cohort, was first selected randomly from the entire study cohorts of CYD14, CYD15, and CYD23/57. Subjects with an event of interest (VCD, HVCD and SVCD) but not selected in the sub-cohort were then included in the case-cohort analysis. Approximately 10% of the total cohort were included. Subjects from CYD23/57 were included in the sub-cohort, but in the end, this study is not part of the NS1 Supplemental Analyses, as retesting of the samples was not allowed as per ICF.

The case-cohort design is a specific type of case-control design where the cases are the same cases as would be included in a cohort study, and controls consist of a random sample selected from the entire source population that gives rise to the cases (i.e. the full cohort). The sample must be representative of the population giving rise to cases (the source population). Such design allows for the estimation of risk ratios (i.e. when the sample is randomly selected from the source population the risk ratio computed using the sample equals the risk ratio computed within the entire cohorts). An advantage of a case-cohort study is that the same random sub-cohort can be used as the comparison group for studying different endpoints, rather than identifying a new set of controls for each endpoint. The CHMP considered that the case-cohort design is thus particularly well suited for the present study. In addition, this design

is much more efficient than the corresponding cohort design, as a sample much smaller than the full cohort generally results in only a marginal loss in statistical power (the statistical power is mostly determined by the number of subjects with the event).

Classification of cases:

Four statistical approaches were used to assess serostatus, and therefore to classify subjects as dengue seropositive or seronegative.

These analyses (hereafter referred to as the NS1 Supplemental Analyses), primarily used 2 different approaches:

MI PRNT50 M0: PRNT50 results either measured or imputed: PRNT50 results at Month 0, either measured (for subjects included in the Immunogenicity Subset) or predicted (multiple imputation of PRNT50) based on anti-NS1 values at M13 and covariates such as age, sex, country, and treatment group using a multiple imputation model (for subjects not included in the Immunogenicity Subset for whom baseline serostatus data were not available). Imputation of PRNT50 serostatus was undertaken by a logistic regression for the MI method.

Anti-NS1 antibody titer at M13 using a cut-off threshold of ≥ 9 EU/mL (NS1 [Thr9] M13): NS1 (Thr9) M13: measured M13 anti-NS1 titers with cut-off thresholds ≥ 9 (EU)/mL.

In addition, 2 other approaches to determine participant's baseline dengue serostatus were used to assess VE during the active surveillance phase and during the SEP. These analyses were conducted to increase the specificity (i.e. to reduce the number of participants wrongly classified as baseline seropositive) and therefore, to improve assessment of vaccine performance, particularly in the younger population:

MI PRNT90 M0: PRNT90 results either measured or imputed: PRNT90 results at Month 0, either measured (for subjects included in the Immunogenicity Subset) or predicted using a multiple imputation model (for subjects not included in the Immunogenicity Subset for whom baseline data were not available).

Anti-NS1 antibody titer at M13 using a cut-off threshold ≥ 50 EU/mL (NS1 [Thr50] M13): NS1 (Thr50) M13: measured M13 anti-NS1 titers with cut-off thresholds ≥ 50 (EU)/mL.

NS1 Supplemental Analyses consisted of a series or 3 consecutive analyses/reports (CSRs), so called, by order: NS1 original, NS1 Extended, and NS1 Close-out. In this document, the NS1 Supplemental Analyses refers mainly to the NS1 Close-out report to gather the most comprehensive dataset.

The accuracy of the imputation approach was evaluated using cross-validation by comparing the predicted baseline serostatus with observed baseline serostatus in the Immunogenicity Subset, for both PRNT50 and PRNT90.

Approaches used in the NS1 Supplemental Analyses to classify subjects as dengue seropositive:

The CHMP noted that four approaches were used in the NS1 Supplemental Analyses to classify subjects as dengue seropositive or seronegative at baseline.

Two approaches were referred as 'primary'. The first one (MI PRNT50 M0) used PRNT50 results at Month 0, either measured (for subjects included in the Immunogenicity Subset) or predicted by a multiple imputation model based on anti-NS1 ELISA values at M13 and covariates (for subjects not included in the Immunogenicity Subset). The second (NS1 [Thr9] M13) used measured anti-NS1 ELISA antibody titers at M13 with a threshold of ≥ 9 (EU)/mL. These two methods were used in the previously presented NS1 Supplemental Analyses, and in particular to explore the safety issue in seronegative individuals.

Two additional approaches were used: PRNT90 results at Month 0 (MI PRNT90 M0) either measured or imputed (similar as the approach for PRNT50) and anti-NS1 antibody titers measured at M13 (NS1 [Thr50] M13) with a thresholds of ≥ 50 (EU)/mL. These two additional methods are more appropriate in the present context, as by using more specific assays, they limit the probability of naïve subjects being wrongly classified as baseline seropositive. Although these methods are more adequate for correctly identifying those previously exposed to dengue, the real false positive rate remains uncertain.

Dengue anti-NS1 IgG ELISA assay:

The CHMP acknowledged that the dengue NS1 IgG ELISA assay, originally developed by University of Pittsburg (Pittsburg, PA, USA) was optimized by Sanofi Pasteur's Global Clinical Immunology (GCI) Department. This assay measures total IgG antibodies against the NS1 protein of the four dengue virus serotypes by ELISA. Due to the lack of standardised methods to assess the performance of assays (in particular the lack of reference samples, or criteria for the selection of reference samples), specificity and sensitivity of the assay are considered uncertain. Moreover, the time since infection and the epidemiological context influence sensitivity and specificity. Specificity is expected to be influenced by the circulation of other flaviviruses, as dengue IgG ELISA assays commonly present cross-reactivity with other flaviviruses. According to published data and data presented previously by the MAH, there is low cross-reactivity when subjects were previously vaccinated with JEV or YFV, and noticeable cross-reactivity for subjects previously infected with ZIKV or West Nile virus (WNV) (Nascimento EJM et al. Development of an anti-Dengue NS1 IgG ELISA to Evaluate Exposure to Dengue Virus, Journal of Virological Methods, 2010). Regarding the potential interference of dengue NS1-specific IgG to Zika, it has to be noted that assessment of dengue serostatus was performed on M13 blood samples, which were taken before Zika epidemics in Latin America, so with no impact on the results. It is unclear how the circulation of various flaviviruses could have influenced the NS1 study results according the local epidemiology (such as tick-borne encephalitis (TBE), Usutu, and Ilheus virus a flavivirus circulating in Latin America).

The vaccine contains NS1 genes from the YF virus. Therefore, the Dengue anti-NS1 IgG ELISA assay is theoretically adequate to differentiate immunity induced by CYD vaccination from that induced by natural dengue infection, and previous exposure to CYD Dengue Vaccine was not expected to induce meaningful levels of antibody against the dengue NS1 protein. However, in the original NS1 Supplemental study, an influence of CYD vaccination on the read-out was observed. To address the potential differential misclassification bias associated with CYD effect on anti-NS1 readout at M13, the MAH used the baseline (M0) PRNT50 dengue antibody values, either measured or predicted (when measured value not available). The prediction was based on a model which used Dengue anti-NS1 ELISA values at M13 and other covariates such as age, sex, country, indicator of whether subject had VCD between M0 and M13, time between onset of VCD case and M13 sample collection date, and treatment group as predictors. The model used for the imputation was fitted in the immunogenicity subset using baseline serostatus (negative or positive) as dependent variable. Prediction of M0 PRNT50 was undertaken using multiple imputation (MI) and SuperLearner methods.

Statistical methods

Vaccine efficacy results were presented for both Immunogenicity Subset and NS1 Supplemental Analyses. The results presented include the following age groups in support to the claimed indication: 9 to 16 years, 6 to 8 years, and 6 to 16 years. For subjects aged 6 to 8 years, analyses of VE against VCD cases due to any serotype are presented along with those for the 2 to 5 years age group in order to provide some perspective on VE in the younger age group.

Results from the Immunogenicity Subset include data from all 3 efficacy studies. Individual estimates for the 2 pivotal efficacy studies CYD14 and CYD15 and the integrated estimate from the pooled analysis of CYD14 + CYD15 are presented. As the outcome measures for efficacy were identical and the results from the 2 Phase III efficacy studies were highly consistent across studies, the integrated efficacy analysis estimates are considered as robust data supporting results from individual studies. A Cox regression model including the study-by-group interaction was used to test heterogeneity and showed that results were consistent. The individual estimate for proof-of-concept study CYD23 and the integrated estimate from the pooled analysis on CYD14 + CYD15 + CYD23 or CYD14 +CYD23 are also provided as supportive data. The same statistical methodology was used to assess VE against symptomatic VCD cases, HVCD cases, and SVCD cases during both the Active Phase and the SEP. VE estimates are considered conclusive when the lower bound of the CI is above 0.

The NS1-related analyses presented in this document were based on those included in NS1 Close-out Report. They are fully aligned with the ones used for the Immunogenicity Subset, with the following specifications:

- MI PRNT50 M0 and MI PRNT90 M0 methods included all cases from M0 to M25 during the Active Phase and allowed estimating VE during the whole Active Phase (D0-M25).
- NS1 (Thr9) M13 and NS1 (Thr50) M13 methods excluded VCD cases from M0 to M13. The methods allowed estimating VE from PD3 until the end of Active Phase (M13-M25).
- Results from the NS1 Supplemental Analyses only include results from the Phase III efficacy trials (CYD14 and CYD15). Data on CYD23 are not included because future testing of samples collected for purposes unrelated to the study objectives was more restrictive in that study; therefore, retest of samples for objectives related to VE against symptomatic VCD was not possible.

Impact of occurrence of dengue infection prior to M13:

The CHMP noted that subjects naïve at baseline and who presented a dengue episode between M0 and M13 were classified as seropositives by the anti-NS1 readout at M13.

Therefore, the evaluation of efficacy was performed from PD3 until the end of Active Phase (M13-M25) (excluding the events between M0-M13) for the NS1 (Thr9) M13 and NS1 (Thr50) M13 methods.

For the MI PRNT50/90 M0 methods, VE was estimated over the whole Active Phase (D0-M25). The CHMP considered that relying on predicted/imputed M0 PRNT50/90 as a surrogate of prior exposure to dengue was likely to minimise the differential biases as compared with M13 anti-NS1 readouts, especially because the model included as predictor an indicator of whether the subject had VCD between M0 and M13. It is unclear to what extent the bias was corrected, and in addition, the approach was not able to address misclassification of asymptomatic infection occurring between M0 and M13.

VE Calculation for analysis of individual studies

VE = 100* [1- (PCYD / PP)] = 100* [1-((CCYD / NCYD) / (CP / NP))]

where:

- PCYD is the density incidence of dengue in the CYD dengue vaccine Group
- PP is the density incidence of dengue in the Control Group
- CCYD is the number of VCD cases in the CYD dengue vaccine Group
- NCYD is the number of person-year in the CYD dengue vaccine Group
- CP is the number of VCD cases in the Control Group
- NP is the number of person-years in the Control Group

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

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

The following statistics were provided: number of VCD cases, number of person-years at risk, density incidence and 95% CI, VE and 95% CI. CIs for the single proportion were calculated using the exact binomial method (Clopper-Person method, quoted by Newcombe. CIs for VE were calculated using the Exact method described by Breslow & Day.

VE was assessed for a given timepoint and time period, depending on the objective. In addition to VE, the density incidence of VCD cases were calculated according to severity for each or any serotype 28 days after each injection (to the end of the Active Phase), from at least 1 injection (from D0) to the end of Active Phase and from the start of the SEP to the end of the trial (SEP).

RR was defined as the ratio of annualized density incidences in the CYD dengue vaccine Group to the Control Group.

VE Calculation for analysis of pooled studies

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

The Hazard Ratio was obtained using a Cox regression model which included, in addition to treatment group, the study and study-by-group interactions as fixed effects. The Cox regression model was used to calculate the VE (Hazard Ratio reduction) and the 95% CI. The 95% CI of HR and p-value associated with Wald-type test statistic was calculated using the variance estimator by Barlow.

VE Calculation in the NS1 Supplemental Analyses

The VE was estimated using a modified Cox regression model proposed by Prentice. The Prentice model, including the vaccine group as covariate, was used to calculate the hazard ratio (HR). The 95% CI of HR and p-value associated with Wald-type test statistic was calculated using the variance estimator by Barlow.

Vaccine efficacy estimates against HVCD and SVCD cases were obtained from 'hazard ratio' estimates analyzed as part of the safety assessment. The relation between a VE estimate and the corresponding hazard ratio is VE = 100*(1 - Hazard Ratio).

Hazard ratios for HVCD and SVCD disease were estimated based on each serostatus classification approach over the Entire Study period (i.e. from either M0 or M13 until the end of the study), by time period (i.e. Active Phase, Year 1 of Hospital Phase, Year 2 of Hospital Phase, and Beyond Year 2 of Hospital Phase), and by study phase (i.e. Active Phase, Hospital Phase, and SEP).

VE estimates against HVCD and SVCD cases over the Active Phase were calculated using analyses by time period. VE estimates over the SEP were calculated using analyses by study phase. A Cox proportional hazard model with time-dependent explanatory variables was used, with interactions between treatment group and time period or study phase introduced in the model.

Handling of Missing Data

Febrile episodes without virological confirmation were not considered in the analysis of VCD cases. No test or search for outliers was performed.

VCD cases:

- If the NS1 test was positive and the DS dengue RT-PCR was missing (or, the other way around) for the same fever episode, the episode was considered as a VCD case.

- If the NS1 test was missing and the DS dengue RT-PCR was negative or missing (or, the other way around) for the same fever episode, the episode was not considered as a VCD case.

The CHMP noted that Vaccine Efficacy results were presented by age category in seropositive subjects, for both Immunogenicity Subset and NS1 Supplemental Analyses. VE analyses are presented in the new target age category (6 to 8 years) and also for subjects aged 9 to 16 years (benchmark) and 2 to 5 years age group, to provide a comprehensive view of efficacy in baseline seropositive subjects.

Data were provided by study and pooled for CYD14 and CYD15. The CYD23 data and the pooled analysis on CYD14 + CYD15 + CYD23 or CYD14 +CYD23 are also provided as supportive data. As the endpoints were similar and the results from the 2 Phase 3 efficacy studies were highly consistent across studies, the integrated efficacy analysis estimates are considered robust.

CYD23/57 was not included in the NS1 Supplemental Analyses (as consent from these subjects could not be obtained for retesting).

The MAH described general methods for the estimation of efficacy in the Immunogenicity Subset. In the individual studies, incidence densities were estimated for each group, for the Active Phase and the SEP. For subjects with several episodes, only the first episode of VCD was included in the analysis of VE. VE was calculated using the incidence densities. In the pooled analyses, VE was calculated as the Hazard Ratio (HR) reduction using the HR obtained with a Cox regression model which included, in addition to treatment group, the study and study-by-group interactions.

In the NS1 Supplemental Analyses, VE was estimated by using HR estimated with a modified Cox regression model proposed by Prentice.

VE estimates are considered conclusive when the lower bound of the CI is above 0.

A similar approach was used for safety by computing RR defined as the ratio of annualized density incidences (individual studies), or HRs (pooled analyses and NS1 Supplemental Analyses). RRs for HVCD and SVCD were estimated over the Entire Study period (i.e. from either M0 or M13 until the end of the study), by time period (i.e. Active Phase, Year 1 of Hospital Phase, Year 2 of Hospital Phase, and Beyond Year 2 of Hospital Phase), and by study phase (i.e. Active Phase, Hospital Phase, and SEP).

Vaccine efficacy estimates against HVCD and SVCD (Active Phase and SEP) were obtained from HR estimates analyzed as part of the safety assessment.

Definition of the Study Populations

Statistical populations from the individual studies were clinically similar, therefore, the statistical analysis sets were transposed for the integrated analysis.

For both safety and efficacy analyses, the FASE from the source trials or subsets of it were utilized.

Full Analysis Set for Efficacy (FASE)

The FASE comprises all subjects who received at least one injection of vaccine or placebo.

Full Analysis Set of Immunogenicity (FASI)

The FASI included all subjects in the Immunogenicity Subset of each trial who received at least one injection and who had a blood sample drawn and a result available after this injection.

This analysis set was used to describe the efficacy according to baseline dengue serostatus during the Active Phase (D0-M25) in the Immunogenicity Subset.

Full Analysis Set for Surveillance Expansion Period (FASSEP)

The FASSEP comprises subjects who received at least one injection and who signed the SEP inform consent. This analysis set was used for VE calculation during the SEP.

This analysis set was used to describe the efficacy according to baseline dengue serostatus during the SEP in the Immunogenicity Subset.

The CHMP noted that, for the efficacy assessments in the Immunogenicity Subset, the populations analysed consist of baseline seropositive subjects from the different age groups included in the FASI and the FASSEP, i.e. subjects from the Immunogenicity Subset during the Active Phase and SEP, respectively. For all safety-related analyses in the NS1 Supplemental Analyses, similar populations were used.

Some aspects of the populations used for the analyses of seropositive subjects (Immunogenicity Subset and NS1 analyses) had to be clarified, both for the efficacy and safety analyses of dengue endpoints (i) The results section states that efficacy results are presented following a 3-dose schedule 6 months apart. This was not consistent with the methods section which refers to all subjects who received at least one injection. In addition, it was not clear whether the approach was different between analyses of efficacy and safety, and between the Immunogenicity Subset and the NS1 analyses. (ii) Overall methods used for the analyses of dengue endpoints (VCD, HCVD or SVCD cases during the Active Phase, Hospital Phase or the SEP) are deemed similar, whether presented as efficacy or safety results, but it was nevertheless not fully clear. The MAH was therefore requested to clarify. In the response, the MAH clearly confirmed that all efficacy and safety analyses on virologically-confirmed dengue (VCD), hospitalized VCD (HCVD) or Severe VCD (SVCD) were performed on subjects who received at least one dose of vaccine or placebo. The MAH acknowledged some erroneous sentences in the SCE. These sentences were corrected. The present assessment report has been updated in line with those corrections.

Summary of main studies

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment.

Table 2: Summary of Integrated analyses of Efficacy for trials CYD14, CYD15 and CYD23/57.

Title: Integrated analyses of efficacy including subjects aged 2 to 16 years from the Phase 3 trials (CYD14 and CYD15) and the Phase 2b PoC (CYD23) trial. Post-hoc analyses in seropositives, stratified by age.	
Study identifier	CYD14, CYD15, CYD23/57.
Design	CYD14 and CYD15 are randomised placebo-controlled Phase 3 efficacy trials. Study CYD23 (and its long term follow up part, study CYD57) is a Phase 2b PoC efficacy trial. All three studies were conducted in highly endemic countries. Studies were similar in terms of study design.

Main Phases	Active Phase (M0 to M25, i.e. approximately until 6 months post-last dose), with an active surveillance of cases. Hospital Phase of 4 years (Year 3 to Year 6), over which only hospitalized dengue cases were searched for. Surveillance expansion phase (SEP) (only CYD14 and CYD15 subjects who re-consented), with a surveillance system similar to the one of the Active Phase (approximately last 2 years of the planned follow-up period, Year 5 and Year 6). Subjects who did not re-consent (approximately 20% of subjects) continued to be followed-up as part of the Hospital Phase.	
Hypothesis	Post-hoc analysis of efficacy (superiority) in seropositive subjects (Immunogenicity Subset and NS1 Supplemental analyses). Efficacy was assessed in the new target population (6 to 8 years), in 2 to 5 years and in 9 to 16 years populations. Data in the overall population 6-16 years were also presented.	
Treatments groups	CYD and Placebo (randomization 2:1). Subjects received at least one dose of Dengvaxia	CYD14: n=10,275 children 2 to 14 years in Asia Pacific (AP) endemic countries; 2000 in the Immunogenicity Subset. CYD15: n=20,869 children 9 to 16 years in LatAm endemic countries; 2000 in the Immunogenicity Subset. CYD23: =4002 children 4 to 11 years in Thailand; 300 in the Immunogenicity Subset. Approximately 70% of the subjects in the Immunogenicity Subset are seropositive (dengue immune).

Note:

Data updated with the final results of CYD14 and CYD15 (5 years follow-up).

Integrated efficacy analyses were performed in seropositive (PRNT50 ≥10 [1/dil] for at least one dengue serotype) subjects from the Immunogenicity Subset. The NS1 Supplemental Analyses are also presented as supportive data. These analyses used an approach to indirectly assess baseline serostatus by testing M13 samples using a dengue anti-NS1 IgG ELISA. A case-cohort design was used. A subcohort of approximately 10% of the total cohorts of CYD14 and CYD15 was included. All subjects with an event of interest (VCD, HVCD and SVCD) were included in the case-cohort analysis. Four approaches were used to classify subjects as dengue seropositive at baseline.

Efficacy data refer to the effect of Dengvaxia on dengue endpoints during Year 1 and 2 (Active Phase), and approximately Year 5-6 (SEP). A similar approach was used to assess the effect of Dengvaxia on HVCD and SVCD during the Hospital Phase. VE extrapolated from RR against HVCD and severe HVCD by periods and over the entire study period are presented in this table although they were considered safety analyses by the MAH.

The efficacy results presented in the table focus on those obtained in the new target population (6-8 years) in comparison to those obtained in the current target population (9-16 years). Efficacy data in 2-5 and 6-16 years groups are not presented in the table.

Endpoints and definitions	Main efficacy endpoint	Virologically confirmed dengue cases due to any serotype during the Active Phase (D0-M25)	VCD any serotype, M0-M25
	Main efficacy endpoint	Virologically confirmed dengue cases due to any serotype during the SEP (approx. Y5-Y6)	VCD any serotype, Year 5-6

	Main efficacy endpoint	Virologically confirmed dengue cases due to each serotype during the Active Phase (D0-M25).	VCD each serotype, M0-M25
	Main efficacy endpoint	Virologically confirmed dengue case cases due to each serotype during the SEP (approx. Y5-Y6)	VCD each serotype, Year 5-6
	Main efficacy endpoint	Hospitalized virologically confirmed dengue case due to any serotype during the Active Phase (D0-M25)	HVCD any serotype, M0-M25
	Main efficacy endpoint	Hospitalized virologically confirmed dengue due to any serotype during the SEP (approx. Y5-Y6)	HVCD any serotype, Year 5-6
	Main efficacy endpoint	Severe virologically confirmed dengue (as per IDMC definition) due to any serotype during the Active Phase (D0-M25)	SVCD any serotype, M0-M25
	Main efficacy endpoint	Severe virologically confirmed dengue (as per IDMC definition) due to any serotype during the the SEP (approx. Y5-Y6)	SVCD any serotype, Year 5-6
	Safety endpoint	HVCD due to any serotype during the Entire Study period	HVCD, entire study
	Safety endpoint	SVCD (as per IDMC definition) due to any serotype during the Entire Study period	SVCD, entire study
	Safety endpoint	HVCD due to any serotype during by study period	HVCD, by period
	Safety endpoint	SVCD (as per IDMC definition) due to any serotype during by study period	SVCD, by period
Database lock	Not provided		

Results and Analysis

Analysis population and time point description	Baseline seropositive subjects included in the FASI and the FASSEP, i.e. subjects from the Immunogenicity Subset during the Active Phase and SEP, respectively. In the FASI, pooled over studies: 236 and 126 seropositive subjects 6-8 years; 1619 and 784 children 9-16 years, and 259 and 115 children 2 to 5 years, respectively in the CYD and Control Groups. Respectively 71% and 67% subjects 6-8 years of age in the CYD and Control Groups remained in the FASSEP. The sub-cohort of the case-cohort NS1 study included a random selection of 10% of the entire study cohorts (n=3578). Of these, 374 were 6-8 years. The proportion of subjects classified as seropositive varied across the methods (62.4%-78.3%). From the subjects of the sub-cohort 92.0% and 77.7% were enrolled in the SEP in CYD14 and CYD15, respectively. All relevant endpoint cases were also included in the case-cohort analyses. In the integrated analyses the 'Active Phase' efficacy endpoints were all cases collected from first dose until the end of the Active Phase. Timepoints, see above.		
Effect estimate per comparison	**VCD any serotype, M0-M25**	**Comparison groups**	**CYD vs. Placebo**
	6-8 years	VE	71.6%
		95%CI	28.9; 88.7
	9-16 years	VE	81.9%
		95%CI	67.2; 90.0

	Supported by the NS1 Supplemental Analyses		
	VCD any serotype, Year 5-6	**Comparison groups**	**CYD vs. Placebo**
	6-8 years	VE	42.8%
		95%CI	-85.4; 81.9
	9-16 years	VE	-22.4%
		95%CI	-247.6; 56.9
	Results not consistent between Immunogenicity Subset and the NS1 Supplemental analyses. NS1 analyses suggest that VE against VCD persists during the SEP (40-65%, LB of 95%CI>0; point estimates similar in both age categories).		
	VCD each serotype, M0-M25	**Comparison groups**	**CYD vs. Placebo**
	6-16 years		
	Serotype 1	VE	76.8%
		95%CI	46.1; 90.0
	Serotype 2	VE	55.5%
		95%CI	-15.3; 82.8
	Serotype 3	VE	89.6%
		95%CI	63.7; 97.0
	Serotype 4	VE	96.5%
			73.4; 99.5
	Analyses by age categories are statistically too imprecise, therefore data are presented for the whole (6-16 years) population. Analyses during the SEP are too imprecise, and are not presented.		
	HVCD any serotype, M0-M25	**Comparison groups**	**CYD vs. Placebo**
	6-8 years	N cases	1 and 5 cases in CYD vs Placebo Groups
		95%CI	NA
	9-16 years	N cases	0 and 6 cases in CYD vs Placebo Groups
		95%CI	NA
	In the NS1 Supplemental Analyses, VE against HVCD ranged between: In 6-8 years, 83.9 % (95% CI: -56.7; 98.3) and 89.4% (95% CI: 8.2; 98.8). In 9-16 years, 91.0% (95% CI: 79.7; 96.0) and 96.4% (95% CI: 88.2; 98.9).		
	HVCD any serotype, Year 5-6	**Comparison groups**	**CYD vs. Placebo**
	6-8 years	N cases	3 and 4 cases in CYD vs Placebo Groups
		95%CI	NA
	9-16 years	N cases	3 and 2 cases in CYD vs Placebo Groups
		95%CI	NA
	In the NS1 Supplemental Analyses, VE against HVCD ranged between: In 6-8 years: 60.8% (95% CI: -10.9; 86.2) and 87.4% (95% CI: 44.0; 97.2). In 9-16 years: 47.4% (95% CI: -15.4; 76.0) and 70.9% (95% CI: 24.2; 88.9).		
	SVCD any serotype, M0-M25	**Comparison groups**	**CYD vs. Placebo**
	6-8 years	N cases	0 and 1 case in CYD vs Placebo Groups
		95%CI	NA
	9-16 years	N cases	0 and 2 cases in CYD vs Placebo Groups
		95%CI	NA
	In the NS1 Supplemental Analyses, VE against SVCD ranged between: In the 6-8 years : 46.2% and 80.0% (not computed for all methods), not conclusive. In the 9-16 years, number of cases too limited in the CYD group to reliably estimate Hazard Ratios.		
	SVCD any serotype, Year 5-6	**Comparison groups**	**CYD vs. Placebo**
	The number of subjects with a SVCD was very low and precluded the calculation of VE. The data do not suggest an increased risk associated with vaccination, for both the subcategories 6-8 years and 9-16 years.		
	HVCD, Entire study	**Comparison groups**	**CYD vs. Placebo**

	All HVCD RRs are <1 in the Immunogenicity subset over the entire study period. RR tended to increase (i.e. be closer to 1) with decreasing age. In subjects 6 to 16 years, the RR estimate was 0.310 (conclusive), corresponding to a VE against HVCD of 69%. In the NS1 Supplemental Analyses: -In subjects aged 6 to 8 years, HVCD RRs ranged from 0.210 to 0.404 (59.6% to 79.0%). -In subjects aged 9 to 16 years, HVCD RRs ranged from 0.129 to 0.213 (78.7% to 87.1%). The upper bound of the 95% CI around the RR was <1 for each estimate.		
	SVCD, Entire study	**Comparison groups**	**CYD vs. Placebo**
	In the Immunogenicity Subset, a trend toward a lower risk of SVCD in the CYD vs the Placebo group was observed over the Entire Study (upper bound of the CI above 1). In the NS1 Supplemental Analyses: -In subjects aged 6 to 8 years, SVCD RRs ranged between 0.22 and 0.40 (VE 60% to 78%). -In children 9-16 years, SVCD RRs ranged from 0.10 to 0.17 (VE 83% to 90%). All RRs were conclusive (except for one of the 4 methods in children 6-8 years).		

Discussion on clinical efficacy

To support this extension of indication to younger age groups, the MAH presented the integrated analyses of efficacy including subjects aged 2 to 16 years from the Phase 3 efficacy trials (CYD14 and CYD15) and from the Phase 2b PoC (CYD23) trial. The data were updated with the final results of the 2 pivotal efficacy studies CYD14 and CYD15 for which data of 5 years follow-up after the last dose are now available. In addition to the efficacy data in the new target population of the claimed indication (children 6 to 8 years), the MAH presented efficacy data in children 9-16 years (benchmark) and 2-5 years, to provide a comprehensive view, and to update results from the prior submission. Data in the overall population 6-16 years (i.e. all available efficacy data supporting the proposed indication) are also presented. Efficacy data in the new target population of the claimed indication (children 6 to 8 years) and in children 2-5 years are mainly data from CYD14 (and limited data from CYD23), while data in children 9-16 years are both from CYD14 and CYD15.

As the indication is restricted to subjects with evidence of prior dengue virus infection, the efficacy analyses focused on seropositive subjects. Therefore, these analyses are limited to subjects for whom baseline serostatus data are available (Immunogenicity Subset). Dengue seropositivity was defined as a neutralizing Ab level ≥ 10 1/dil against at least one dengue serotype measured by PRNT50. Importantly, the NS1 Supplemental Analyses are also presented as supportive data, as this allowed an assessment on a larger number of cases.

Long-term data analyses related to hospitalised dengue are presented in the safety section but discussed together with the efficacy data in this section.

Design and conduct of clinical studies

Design of the three Efficacy Studies:

CYD14 and CYD15 are randomised placebo-controlled Phase 3 efficacy studies. These trials randomized (in a 2:1 CYD:Placebo ratio) respectively 10,275 children 2 to 14 years in Asia Pacific (AP) endemic countries and 20,869 children 9 to 16 years in LatAm endemic countries. Study CYD23 is a Phase 2b PoC efficacy study conducted in Thailand among 4002 children 4 to 11 years (also randomized in a 2:1 CYD:Placebo ratio).

In these studies, there was an 'Active Phase' (from M0 to M25), over which an active surveillance of cases was performed. This phase was followed by an Hospital Phase of 4 years (Year 3 to Year 6), over which only hospitalized dengue cases were searched for. Following the acknowledgment of the safety issue (increased risk of severe dengue in sero-naïve individuals) by the MAH (end of Year 4), a surveillance system similar to the one of the Active Phase ('surveillance expansion phase' [SEP]) was set up. The SEP was restricted to subjects from CYD14 and CYD15. No SEP was instituted in CYD23/57 (CYD57 being the follow-up study of study CYD23), as this study was already completed at that time. The SEP started more than 2 years after the end of the Active Phase, at various times depending of the time of protocol approval and the time required to ask re-consent from the subjects. The SEP lasted approximately the last 2 years of the planned follow-up period in CYD14 and CYD15 (Year 5 and Year 6) and allowed for persistence of efficacy assessment. Subjects who did not re-consent (approximately 20% of subjects) continued to be followed-up as part of the Hospital Phase.

Studies were similar in terms of study design. CYD14 and CYD15 used the same endpoints definitions, supporting the pooled analyses. The CYD23 used a slightly different dengue case definition, laboratory methods and testing algorithm (see below).

The main limitations of the efficacy trials as identified in previous assessments are as follows:

- The trials did not aim to assess the effect of CYD on VCD and severe VCD according to dengue immune serostatus at baseline, and more generally, according to flaviviruses serostatus at baseline. The number of subjects for whom dengue serostatus was determined (by PRNT50) at baseline is limited: approximately 7.5% (N=300), 10% (N=2000), and 20% (N=2000) of study participants in CYD23/57, CYD15, and CYD14, respectively.

- Efficacy data were to be collected during the Active Phase only i.e. up to 1 year post-last vaccine injection. The Hospital Phase was conceived to assess long-term safety only (detection of signals of enhanced disease). In line with this approach, past the first year post dose 3, only hospitalised cases were detected, and surveillance methods were weakened.

Overall, this implied that data on the long-term effect of CYD on clinically meaningful endpoints (including severe dengue) and in relevant subgroups (i.e. according to serostatus and age at baseline) could not be generated. This was considered as a weakness given that enhanced disease is more likely to occur in naïve individuals, when protective immunity wanes.

To address these limitations, at the end of Year 4, the MAH set up a protocol amendment allowing for a more active follow up of dengue on the long term (SEP). The MAH also extended the number of available data on baseline serostatus by using post-hoc analyses (see NS1 Supplemental Analyses, below in this section).

Objectives:

The main objectives of the efficacy analyses performed to support this extension of indication are similar in the Immunogenicity Subset and the NS1 Supplemental analyses and consistent with the previous Integrated Efficacy Analyses. Efficacy was assessed in dengue seropositive subjects aged 2 to 5 years, 6 to 8 years and 9 to 16 years, during the whole Active Phase (M0-M25) and the SEP (from the time of consent until the end of the study). Efficacy in preventing the occurrence of VCD due to any serotype and to each serotype was assessed. Efficacy in preventing HVCD and SVCD (as per IDMC definition) was also assessed during these periods.

Efficacy data thus refer to the effect of Dengvaxia on dengue endpoints during Year 1 and 2 (Active Phase), and approximately Year 5-6 (SEP). A similar approach (analyses in the Immunogenicity Subset, supported by NS1 Supplemental Analyses) was used to assess the effect of Dengvaxia on hospitalised dengue and severe hospitalised dengue during the Hospital Phase. RR against HVCD and severe HVCD

are presented. This was considered as safety analyses by the MAH (instead of efficacy). This distinction between efficacy and safety data is artificial, but reflects the initial design of the studies.

Endpoints:

Efficacy endpoints include symptomatic virologically-confirmed dengue (VCD), severe virologically-confirmed dengue (SVCD) as ascertained by the IDMC and hospitalized virologically-confirmed dengue (HVCD), due to any and to each serotype, occurring during the Active Phase and during the SEP. HVCD and hospitalised SVCD during the Hospital Phase were collected as part of the safety endpoints.

Detection of VCD and HVCD cases over the study phases:

The Active Phase started on the day of the first dose and lasted until 13 months after the third injection. This Phase includes an intensive surveillance in order to maximize the detection of all symptomatic VCD episodes. This included school-based surveillance, and reminders to the participants through phone calls/SMS or home visits. The Hospital Phase (approximately Year 3 to Year 6) started at the end of the Active Phase and ended up to 5 years after the third injection. During this period only hospitalized and severe hospitalized dengue cases were collected. The collection of events was based on surveillance of both study and non-study healthcare sites. There was a minimum frequency of one contact every 3 months. During the SEP (approximately Year 5 and Year 6), a surveillance system similar to the one of the Active Phase (SEP) was set up.

Efficacy endpoints, definition and ascertainment methods:

Symptomatic VCD was defined as an acute febrile episode virologically confirmed by dengue reverse transcriptase polymerase chain reaction (RT-PCR) and/or dengue NS1 enzyme linked immunosorbent assay (ELISA) antigen test, in line with WHO recommendation. In case of a febrile episode, 2 blood samples were to be collected (a first as soon as possible and a second 7-14 days after the acute sample). RT-PCR assays for dengue are highly sensitive and specific if performed on early samples. The NS1 ELISA Ag assay is less sensitive and less specific than RT-PCR assays during the very few days after symptom onset, but is useful to identify dengue on samples collected later (days 4 and 5). Virologically-confirmed cases were serotyped. Overall, the protocol definition and assessment methods for VCD were considered appropriate. However, misclassification between dengue and other flaviviruses remains a possibility. It is not known whether this could have affected the VE results (by dilution), particularly during the SEP due to the zika outbreak in LatAm (CYD15 results).

Severe VCD (SVCD) as ascertained by the IDMC was defined as VCD accompanied by at least one severity criteria: (i) Low platelet count with bleeding and plasma leakage, (ii) Shock, (iii) Bleeding requiring blood transfusion, (iv) Encephalopathy, (v) Liver impairment, (vi) Impaired kidney function, (vii) Myocarditis, pericarditis or clinical heart failure. The IDMC definition was supported as it takes into account the 1997 and 2009 WHO definitions. The Independent Data Monitoring Committee (IDMC) evaluated all VCD/HVCD for severity according to pre-defined criteria. The definition of SVCD was identical between all phases, as well as the review process by the IDMC. However, due to differences in the surveillance systems, severe cases were identified among all VCD cases during the Active Phase and the SEP but only among hospitalized cases during the Hospital Phase. There were few cases assessed as severe without having been hospitalized.

Hospitalized VCD (HVCD) was defined as any VCD case leading to hospitalization. This endpoint presents several limitations: (i) The rate of hospitalisation of VCD depends on local practices (in CYD14, this rate varied from 6% in Vietnam to 46% in Indonesia during the Active Phase); (ii) A high level of protocol deviations occurred in the Hospital Phase. For ex. acute samples were not collected within 5 days for the PCR confirmation of dengue (as required per protocol) in 2% of the subjects during the Active Phase and 18% of the Year 3 (1st year of the Hospital Phase); (iii) The annual detection rate of hospitalization for

VCD decreased between the Active and Hospital phases in the placebo group, raising the hypothesis of an underdetection/underreporting of (severe) HVCD during the Hospital Phase as compared to the Active Phase. Although data collected during the Hospital Phase are less robust than in the Active Phase, data on hospitalised dengue are very informative with respect to the duration of protection.

Endpoints in individual vs pooled analyses:

Endpoints definitions used in the analyses performed to support this extension of indication are corresponding to those of each individual study. The endpoint definitions were similar over the 3 efficacy studies. Only slight differences in the definition of fever were noted between CYD14/CYD15 and CYD23, as well as a slight difference in the timepoint for the second blood sample (within 7 days of the onset of fever in CYD23, within 5 days of the onset of fever in CYD14 and CYD15). The methods for serotype identification slightly varied between CYD14/CYD15 and CYD23.

In the primary analysis of each trial, the primary endpoint observation period extended from 28 days after the third dose up to the end of the Active Phase (period M13-M25). This differs from the integrated analyses in which the 'Active Phase' efficacy endpoints were all cases collected from the first dose until the end of the Active Phase. This might potentially have led to an underestimation of the VE. The 'SEP' efficacy endpoints used in the integrated analyses were all cases collected from date of subject re-consented until the end of the study.

Additional analyses

NS1 Supplemental Analyses:

The MAH performed the NS1 Supplemental Analyses, which confirmed the safety issue in seronegatives. The NS1 Supplemental Analyses aimed at obtaining efficacy and relative risk estimates according to dengue serostatus in the efficacy trials. These analyses are provided for seropositives in the present application, updated with the full FU period.

Given that the majority of study participants had no pre-vaccination blood sample, the MAH developed an approach to indirectly assess baseline serostatus by testing M13 samples (i.e. 1 month after the third vaccine dose), as these samples were taken in all subjects. PRNT assay could not be used as it is not able to distinguish immunity induced by vaccination and prior dengue infection. Therefore, the MAH developed a dengue anti-nonstructural protein 1 (NS1) IgG enzyme-linked immunosorbent assay (ELISA). This NS1 assay aims at differentiating anti-NS1 antibodies induced by wild-type dengue infection from those induced by vaccination (since the CYD dengue vaccine contains genes encoding NS1 from the yellow fever 17D vaccine virus rather than from dengue virus).

The dengue NS1 IgG ELISA assay measures total IgG antibodies against the NS1 protein of the four dengue virus serotypes by ELISA. As part of previous assessments, it was considered that due to the lack of standardised methods to evaluate the performance of assays (lack of reference samples or criteria for their selection), specificity and sensitivity of the assay are not known. Moreover, the time since infection and the epidemiological context influence sensitivity and specificity. Specificity is expected to be largely influenced by the circulation of other flaviviruses, as dengue IgG ELISA assays commonly present cross-reactivity with other flaviviruses. Regarding the potential interference of dengue NS1-specific IgG to Zika, it has to be noted that the M13 blood samples were taken before Zika epidemics in Latin America, so with no impact on the results. It is unclear how the circulation of various flaviviruses could have influenced the NS1 study results according the local epidemiology.

The vaccine contains NS1 genes from the YF virus. Therefore, the Dengue anti-NS1 IgG ELISA assay is theoretically adequate to differentiate immunity induced by CYD vaccination from that induced by natural dengue infection. Previous exposure to CYD vaccine was not expected to induce meaningful levels of

antibody against the dengue NS1 protein. However, in the original NS1 Supplemental study, an influence of CYD vaccination on the read-out was observed. To address the potential differential misclassification bias associated with CYD effect on anti-NS1 readout at M13, the MAH used the baseline (M0) PRNT50 dengue antibody values, either measured or predicted (when measured value not available). The prediction was based on a model which used Dengue anti-NS1 ELISA values at M13 and other covariates such as age, sex, country, indicator of whether subject had VCD between M0 and M13, time between onset of VCD case and M13 sample collection date, and treatment group as predictors. The model used for the imputation was fitted in the Immunogenicity Subset using baseline serostatus (negative or positive) as dependent variable. Prediction of M0 PRNT50 was undertaken using multiple imputation (MI) and SuperLearner methods.

A case-cohort design was used. A sample of subjects, referred to as the sub-cohort, was first selected randomly from the entire study cohorts of CYD14, CYD15, and CYD23/57. Subjects with an event of interest (VCD, HVCD and SVCD) but not selected in the sub-cohort were then included in the case-cohort analysis. Approximately 10% of the total cohorts was included. Subjects from CYD23/57 were included in the sub-cohort, but in the end, this study is not part of the NS1 Supplemental Analyses, as retesting of the samples was not allowed as per ICF.

The design was assessed previously. Briefly, the case-cohort design is a specific type of case-control design where the cases are the same cases as would be included in a cohort study, and controls consist of a random sample selected from the entire source population that gives rise to the cases. Such design allows for the estimation of risk ratios (when the sample is representative from the source population, the risk ratio computed using the sample equals the risk ratio computed within the entire cohorts). An advantage of a case-cohort study is that the same sub-cohort can be used as the comparison group for studying different endpoints, rather than identifying a new set of controls for each endpoint. The case-cohort design is thus particularly well suited for the present situation. In addition, this design is much more efficient than the corresponding cohort design, as a sample much smaller than the full cohort generally results in only a marginal loss in statistical power (the statistical power is mostly determined by the number of subjects with the event).

For the present extension of indication, four approaches were used in the NS1 Supplemental Analyses to classify subjects as dengue seropositive or seronegative at baseline. Two approaches were referred as 'primary'. The first one (MI PRNT50 M0) used PRNT50 results at Month 0, either measured (for subjects included in the Immunogenicity Subset) or predicted by a multiple imputation model based on anti-NS1 ELISA values at M13 and covariates (for subjects not included in the Immunogenicity Subset). The second (NS1 [Thr9] M13) used measured anti-NS1 ELISA antibody titers at M13 with a threshold of ≥9 EU/mL. These two methods were used in the previously presented NS1 Supplemental Analyses to explore the safety issue in seronegative individuals. Two additional approaches were used: PRNT90 results at Month 0 (MI PRNT90 M0) either measured or imputed (similar as the approach for PRNT50) and anti-NS1 antibody titers measured at M13 (NS1 [Thr50] M13) with a threshold of ≥50 EU/mL. These two additional methods are more appropriate in the present context, as by using more specific read-outs, they limit the probability of naïve subjects being wrongly classified as baseline seropositive. Although these methods are more adequate for correctly identifying those previously exposed to dengue, the real false positive rate remains uncertain.

Subjects naïve at baseline and who presented a dengue episode between M0 and M13 are classified as seropositives by the anti-NS1 readout at M13. Therefore, the evaluation of efficacy was performed from post-dose 3 until the end of Active Phase (M13-M25) (excluding the events between M0-M13) for the NS1 (Thr9 and Thr50) M13 methods. For the MI PRNT50/90 M0 methods, VE was estimated over the whole Active Phase (D0-M25). Compared to M13 anti-NS1 value, relying on predicted/imputed M0 PRNT50/90 as a surrogate of prior exposure to dengue is likely to minimise the differential biases,

especially because the model included as predictor an indicator of whether the subject had VCD between M0 and M13. It is unclear however to what extend the bias was corrected, especially because the approach was not able address misclassification of asymptomatic infection occurring between M0 and M13.

Statistical analyses:

Data are provided by study and pooled for CYD14+CYD15. The CYD23 data and the pooled analysis on CYD14+CYD15+CYD23 or CYD14+CYD23 are also provided as supportive data. As the endpoints were similar and the results from the 2 Phase 3 efficacy studies were highly consistent across studies, the integrated efficacy analysis estimates are considered robust.

In the Immunogenicity Subset, incidence densities were estimated for each group, for the Active Phase and the SEP in the individual studies. For subjects with several episodes, only the first episode of VCD was included in the analysis of VE. VE was calculated using the incidence densities. In the pooled analyses, VE was calculated as the Hazard Ratio (HR) reduction using the HR obtained with a Cox regression model which included, in addition to treatment group, the study and study-by-group interactions. In the NS1 Supplemental Analyses, VE was estimated by using HR estimated with a modified Cox regression model proposed by Prentice. VE estimates are considered conclusive when the lower bound of the 95%CI is above 0.

A similar approach was used for safety estimations by computing RR defined as the ratio of annualized density incidences (individual studies), or HRs (pooled analyses and NS1 Supplemental Analyses). RRs for HVCD and SVCD were estimated over the Entire Study period (i.e. from either M0 or M13 until the end of the study), by time period (i.e. Active Phase, Year 1 of Hospital Phase, Year 2 of Hospital Phase, and beyond Year 2 of Hospital Phase), and by study phase. VE estimates against HVCD and SVCD (Active Phase and SEP) were obtained from HR estimates analyzed as part of the safety assessment.

All efficacy and safety analyses were performed on subjects who received at least one dose of vaccine or placebo. For the efficacy assessments in the Immunogenicity Subset, the populations analysed consist of baseline seropositive subjects from the different age groups included in the FASI and the FASSEP, i.e. subjects from the Immunogenicity Subset during the Active Phase and SEP, respectively.

Results

Description of Study Populations:

For the Immunogenicity Subset analyses (FASI, pooled over studies), there were 236 and 126 seropositive subjects 6-8 years respectively in the CYD and Control Groups (mainly CYD14, also CYD23/57). There were 1619 and 784 children 9-16 years (all studies, mainly CYD15), and 259 and 115 children 2 to 5 years (CYD14 and CYD23/57), in respective groups. Respectively 71% and 67% subjects 6-8 years of age in the CYD and Control Groups remained in the FASSEP. Age and gender were balanced between groups, within each study, and within age categories. Most of the 6-8 years old population originates from CYD14, as there were no children of this age in CYD15.

The sub-cohort of the case-cohort NS1 study included a random selection (stratifying for age and trial site) of 10% of the entire study cohorts. This represented 3578 subjects irrespective of serostatus and age (CYD14, n=1099; CYD15, n=2130; CYD23/57, n=349). Of these 3578 subjects, 374 were 6-8 years. The percentage of subjects included from each group (CYD and Control Groups) was similar. As explained in study methods, all relevant cases were also included in the case-cohort analyses. Subjects from the CYD23 were at the end not included in the NS1 Supplemental analyses (consent could not be obtained for retesting, see above). From the subjects of the sub-cohort 92.0% and 77.7% were enrolled in the SEP in CYD14 and CYD15, respectively. The proportion of subjects classified as seropositive varied across

the method used. In subjects aged 6-16 years these proportions were respectively in the CYD and Placebo Groups: 78.3% and 76.2% with MI PRNT50 M0, 71.9% and 72.4% with MI PRNT90 M0, 79.6% and 77.7% with NS1 (Thr9) M13, and 67.9% and 62.4% with the NS1 (Thr50) M13. As expected, percentages were lower with the more specific methods.

Vaccine Efficacy against VCD due to any serotype during the Active Phase:

VE against VCD during the Active Phase tends to be lower in children 6-8 years of age (71.6% [95%CI: 28.9; 88.7]) and 2-5 year of age (71.6% [95%CI: 20.3; 89.9]) compared to older children 9-16 years (81.9% [95% CI: 67.2; 90.0]) (Immunogenicity Subset, pooled). Confidence intervals are largely overlapping. Results in the Immunogenicity Subset are overall supported by those of the NS1 Supplemental Analyses, and are consistent across methods and studies. Overall, in the population 6-16 years, VE was 79.9 % (95% CI: 66.9; 87.7) (Immunogenicity Subset, pooled).

Vaccine Efficacy against VCD due to any serotype during the SEP:

Results are not consistent between the Immunogenicity Subset and the NS1 Supplemental analyses. Data in the Immunogenicity Subset suggest a lack of efficacy over the SEP, whatever the age category. In contrast, the NS1 analyses suggest that VE against VCD persists during the SEP, similarly in both children 6-8 and 9-16 year of age, although at lower level (40-65%, LB of 95%CI>0 for most estimates) compared to the Active Phase. There were no marked differences across studies. Point estimates were similar in both age categories. In contrast, VE seems not maintained in children 2-5 years of age in the NS1 analyses.

Vaccine Efficacy against VCD due to each serotype during the Active Phase:

Analyses by serotype and age categories are statistically not meaningful (estimates too imprecise). In the overall cohort of children 6-16 years, VCD VE against serotype 2, and to a lesser extent against serotype 1, tends to be lower compared to other serotypes during the Active Phase. This is already described in the SmPC for the 9-16 years children. It is noted that the efficacy results do not match the immunogenicity results (lower immunogenicity for serotype 4).

Vaccine Efficacy against VCD due to each serotype during the SEP:

Results by serotype are not interpretable in the Immunogenicity Subset.

In the pooled NS1 Supplemental Analyses, results tended to vary across studies. Some persisting efficacy was observed for all serotypes in CYD14 (serotype 1: 49.1-73.8%, serotype 2: 59.5-84.5%, serotype 3: 29.1-44.2%, serotype 4: 74.8-83.5%). Levels of efficacy persisting during the SEP varied widely across serotypes in CYD15. In this study, no or very low efficacy persistence is observed for serotypes 1, 2 and 3. In contrast, persistence of efficacy against VCD is observed for serotype 4 during the SEP. Results of VE due to each serotype during the SEP are difficult to interpret due to small numbers and to the possible impact of the Zika outbreak that occurred in Latin America during CYD15.

Overall, in CYD14 and CYD15, dengue-neutralizing antibody levels decrease over time from post-dose 3 through Year 5, for all 4 serotypes. GMTs for each serotype remain at higher levels than baseline. Differences across groups attenuate with time. GMTs at Year 5 remain higher in the vaccinated group vs. the control group, for all 4 serotypes, particularly in CYD14 (see immunogenicity discussion).

The MAH investigated the effects of Zika infection on dengue-neutralizing antibody responses in a post-hoc analysis of data from the CYD15 study.[2] All virologically confirmed Zika episodes were detected during the SEP. Dengue-neutralizing antibody responses were boosted for those who experienced Zika infection (this may at least partly explain why the Zika epidemic was associated with a coincident

[2] Zambrano B, Noriega F, Dayan GH, Rivera DM, Arredondo JL, Reynales H, et al. Zika and Dengue Interactions in the Context of a Large Dengue Vaccine Clinical Trial in Latin America. Am J Trop Med Hyg. 2021;104(1):136-44).

decrease in dengue across the Americas). As the Zika infection attack rate was substantial during the SEP, this affected greatly the overall level of neutralizing antibodies during the SEP and overall GMTs went up during the SEP in both groups. The booster effect of Zika infection was pronounced in the placebo Group, but much less marked (serotype 1 and 3) or not seen (serotype 2 and 4) for those vaccinated. As a consequence, the remaining differences in terms of neutralizing antibodies between the groups are very modest this study, except for serotype 4 for which some difference remains at the end of the SEP. This phenomenon may have influenced efficacy over time in CYD15. However, the actual clinical relevance of the immunogenicity findings by serotype remains unknow, as there is no direct link between serotype-specific immune responses and efficacy for this vaccine. For example, VCD efficacy (Active Phase) against serotype 2, and to a lesser extent against serotype 1, tends to be lower compared to other serotypes. In contrast to efficacy, GMTs tend to be consistently lower for serotype 4 when compared to serotypes 1-3 GMTs. The impact of immunological cross-reactivity between assay on the immunogenicity results is also unclear.

Vaccine Efficacy against HVCD and SVCD due to any serotype during the Active Phase:

In the Immunogenicity Subset, numbers of HVCD and SVCD cases are low and did not allow VE estimations, but in all age categories those numbers are consistent with efficacy (i.e. numbers in favour of CYD vs Placebo).

Although imprecise, all HVCD/SVCD VE point estimates are in favour of CYD, in all age categories in the NS1 Supplemental analyses. VE points estimates were higher compared to those of VE against VCD, and were consistent across methods. HVCD/SVCD VE tended to decrease with decreasing age. In children 6-16 years (NS1 Supplemental analyses, pooled analysis CYD14+CYD15), VE estimates against HVCD ranged between 90.3% (95% CI: 80.1; 95.3) and 95.7% (95% CI: 87.9; 98.5), while VE against SVCD ranged between 91.8% (95% CI: 72.3; 97.6) and 96.8% (95% CI: 75.9; 99.6).

Vaccine Efficacy against HVCD and SVCD due to any serotype during the SEP:

Overall, SEP data are imprecise for HVCD in the Immunogenicity Subset, precluding the calculation of VE. Numbers are not consistent with a safety concern (the case split remains favourable to the vaccine). NS1 Supplemental Analyses suggest that some level of efficacy may be maintained Year 5 and 6 post-vaccination against HVCD, both in children 6-8 and 9-16 years of age. The level of efficacy is consistent with or slightly higher than that seen for VCD efficacy over the SEP. In contrast, data in children 2-5 years suggest a lack of or negative efficacy (HVCD) over the long term.

The number of subjects with a SVCD was very low and precluded the calculation of VE. The data do not suggest an increased risk associated with vaccination, for the overall proposed indication population or for the subcategories 6-8 years and 9-16 years.

Vaccine Efficacy against HVCD due to any serotype by study period:

In the Immunogenicity Subset (pooled studies), there are only few cases, and estimates per period are very imprecise. Estimates are also imprecise in the NS1 analyses for the Hospital Phase, as estimates were computed over one year (instead of 2 for the other Phases).

In the Immunogenicity Subset and in the NS1 analyses, RR point estimates are <1 (decreased risk of HVCD in vaccinated vs. controls for all the periods in children aged 6 to 8 years and aged 9 to 16 years (except for Year 4 in the younger children in the Immunogenicity subset, with a RR of 1.09). During Year 3 and Year 4, RRs were closer to 1 compared to the Active Phase and the SEP, for both age categories. In children 6-16 years, RRs ranged 0.04-0.12 (Active Phase), 0.21-0.33 (Year 3), 0.20-0.38 (Year 4), and 0.23-0.43 (Years 5-6), respectively (NS1 analyses), with conclusive estimates. Overall, these data suggest a decrease in efficacy over time after the Active Phase, and do not point to a safety issue.

Age trend:

Overall, vaccine efficacy tends to be lower with lowering age. It is considered likely that higher proportion of baseline dengue naïve subjects (therefore higher false positive rate) and lower immunity to dengue at baseline, both in terms of magnitude and quality (such as monotypic vs multitypic profile) in younger age categories contribute to this trend.

Age ranges of the enrolled populations, dengue virus serotype as well as other flavivirus circulation vary across studies. Specificity of the PRNT and NS1 assay may also vary across studies (due to local circulation of flaviviruses). The independent effect of age, study region, misclassification of serostatus , and baseline immunity on the efficacy results, is difficult to disentangle.

Conclusions on clinical efficacy

Efficacy was assessed post hoc in seropositive subjects from the Immunogenicity Subset and in the supportive NS1 Supplemental analyses from the CYD14 and CYD15 trials. despite some limitations, results of both the immunogenicity Subset and the NS1 Supplemental analyses suggest efficacy and no safety issue in term of risk of severe dengue, in the 6-8 years as in the 9-16 years.

Up to one year post-dose 3, efficacy against virologically confirmed dengue (VCD) was demonstrated in the new target population (6-8 years), but with wide 95% CI. There is a trend towards lower efficacy in this age group (approximately 70%) compared to the 9-16 years (approximately 80%). Although estimates are imprecise, data suggest efficacy against hospitalised VCD and against severe VCD in all age categories.

The long-term data show that efficacy decreases over time as of Year 3 (after the Active Phase), but do not suggest a risk associated with vaccination, for both the 6-8 years and 9-16 years populations.

The CHMP noted that data are imprecise and inconsistent between the Immunogenicity Subset and the NS1 analyses for the Surveillance Expansion Phase (Year 5-6). The first suggest a lack of efficacy against VCD during that period, while the latter suggest that some level of efficacy may be maintained over Year 5 and Year 6 post-vaccination, against VCD and hospitalised VCD, both in children 6-8 and 9-16 years of age.

Clinical safety

The pooled/integrated safety analysis includes 22 clinical studies used for the evaluation of the CYD dengue vaccine final formulation (i.e. ~5 $\log^{10}$ CCID50 per dose per serotype), in subjects aged ≥6 years irrespective of the vaccination schedule. The 22 clinical studies contributing to the reactogenicity and safety results presented in this document are: 3 Phase I (CYD04, CYD05, and CYD06), 2 Phase IIa (CYD10 and CYD11), 9 Phase II (CYD12, CYD13, CYD22, CYD24, CYD28, CYD30, CYD47, CYD51, and CYD65 [intermediate results – until approximately one year after the primary series]), 2 Phase IIb (CYD23/57), 4 Phase III (CYD14, CYD15, CYD17, and CYD32) and 2 Phase IIIb (CYD71 and CYD67).

The design and objectives of studies recently completed or having achieved a milestone assessing clinical safety (i.e. CYD14, CYD15, CYD65, CYD71, and CYD67) are summarized in the table below. The design and objectives of the other studies contributing to the safety assessment have been provided by the MAH.

Table 3: Overview of Studies Assessing Clinical Safety (studies recently completed or having recently achieved a milestone)

Study Identifier	Location of Study Report	Main Objectives of the Study	Study Design	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Countries; Endemic / Non-endemic Area; Trial Period (FVFS – LVLS*)	Healthy Subjects or Diagnosis of Patients	Study Status; Type of Report
CYD14	5.3.5.1	- Vaccine efficacy against virologically-confirmed symptomatic dengue cases post-dose 3 - Safety throughout the trial and descriptive reactogenicity (injection site and systemic) after each injection, in a subset of subjects. - Descriptive dengue humoral immune response, after the 2nd and 3rd injection, in a subset of subjects. - 5-year post-injection 3 follow-up: safety, detection of confirmed hospitalized dengue cases and antibody persistence in a subset of subjects.	Phase III, randomized, placebo-controlled, blind-observer, multicenter trial.	CYD dengue vaccine (~5 log10CCID50/ serotype 1, 2, 3, 4) Group 1: CYD dengue vaccine at D0, M6 and M12. Group 2: Placebo (NaCl 0.9%) at D0, M6 and M12. 0.5 mL/ injection. Subcutaneous injection	Randomized: 10 275 - Group 1: 6851 - Group 2: 3424	Indonesia, Malaysia, Thailand, the Philippines, Viet Nam Endemic areas 03 Jun 2011 to 21 Nov 2017 (including a 5-year post-injection 3 follow-up)	Healthy subjects 2–14 years	Completed Final CSR
CYD15	5.3.5.1	- Vaccine efficacy against virologically-confirmed dengue cases post-dose 3. - Safety throughout the trial and descriptive reactogenicity (injection site and systemic) after each injection, in a subset of subjects. - Descriptive dengue humoral immune response, after the 2nd and 3rd injection, in a subset of subjects. - 5-year post-injection 3 follow-up: safety, detection of confirmed hospitalized dengue cases and antibody persistence in a subset of subjects.	Phase III, randomized, placebo-controlled, blind-observer, multicenter trial.	CYD dengue vaccine (~5 log10CCID50/ serotype 1, 2, 3, 4) Group 1: CYD dengue vaccine at D0, M6 and M12. Group 2: Placebo (NaCl 0.9%) at D0, M6 and M12. 0.5 mL/ dose. Subcutaneous injection	Randomized: 20 869 - Group 1: 13 920 - Group 2: 6949	Brazil, Colombia, Honduras, Mexico, Puerto Rico Endemic area 08 Jun 2011 to 05 Mar 2018 (including a 5-year post-injection 3 follow-up)	Healthy subjects 9–16 years	Completed Final CSR
CYD65	5.3.4.1	- NI of the dengue humoral immune response to each dengue serotype after a 2-dose schedule compared to a 3-dose schedule in baseline seropositive subjects, 28 days / 1 year after last injection - NI of the dengue humoral immune response to each dengue serotype after a booster dose compared to the last dose of a 3-dose schedule in baseline seropositive subjects - Descriptive dengue humoral immune response to each dengue serotype after the last injection of a 1-, 2-, and 3-dose schedule, 28 days / 1 year after last injection - Safety throughout the trial and descriptive reactogenicity (injection site and systemic) after each injection.	Phase II, randomized, observer-blind, multicentered study	CYD dengue vaccine (~5 log10 CCID50/ serotype 1, 2, 3, 4) Group 1: CYD dengue vaccine at D0, M6, and M12 Group 2: Placebo at D0, CYD dengue vaccine at M6 and M12 Group 3: Placebo at D0 and M6, CYD dengue vaccine at M12 CYD dengue vaccine either 1 year (Groups 1a, 2a, and 3a) or 2 years (Groups 1b, 2b, and 3b) after the primary series. 0.5 mL/injection. Subcutaneous injection.	Randomized: 1050 Group 1: 350 Group 2: 348 Group 3: 352	Colombia and the Philippines Endemic area 02 May 2016 to 20 Dec 2018 (interim CSR)	Healthy subjects 9–50 years	Ongoing Interim CSR (up to 28 days after booster injection at Year 1) Final CSR available in Q1 2021
CYD67	5.3.5.1	- NI of Gardasil humoral immune response after concomitant administration with CYD dengue vaccine compared to sequential administration, after last dose of Gardasil. - NI of the dengue humoral immune response after concomitant administration with Gardasil compared to sequential administration, after last dose of CYD dengue vaccine - Descriptive humoral immune response after each dose of Gardasil - Descriptive humoral immune response after each dose of CYD dengue vaccine - Descriptive safety of Gardasil and the CYD dengue vaccine after each and any injection in each group	Phase IIIb, randomized, open-label, multicenter study	CYD dengue vaccine (~5 log10 CCID50/ serotype 1, 2, 3, 4) Group 1: CYD dengue vaccine + Gardasil at D0 and M6, CYD dengue vaccine at M12 Group 2: Gardasil at D0 and M6; CYD dengue vaccine at M1, M7, and M13 0.5mL/injection CYD dengue vaccine: subcutaneous injection Gardasil: intramuscular injection	Randomized: 528 Group 1: 266 Group 2: 262	Malaysia Endemic area 01 Dec 2016 to 27 May 2019	Healthy subjects 9–13 years	Completed Final CSR
CYD71	5.3.5.1	- NI of Cervarix humoral immune response after concomitant administration with CYD dengue vaccine compared to sequential administration, after last dose of Cervarix. - NI of the dengue humoral immune response after concomitant administration with Cervarix compared to sequential administration, after last dose of CYD dengue vaccine - Descriptive humoral immune response after each dose of Cervarix - Descriptive humoral immune response after each dose of CYD dengue vaccine - Descriptive safety of Cervarix and the CYD dengue vaccine after each and any injection in each group	Phase IIIb, randomized, open-label, multicenter study	CYD dengue vaccine (~5 log10 CCID50/ serotype 1, 2, 3, 4) Group 1: CYD dengue vaccine + Cervarix at D0 and M6, CYD dengue vaccine at M12 Group 2: Cervarix at D0 and M6; CYD dengue vaccine at M1, M7, and M13 0.5mL/injection CYD dengue vaccine: subcutaneous injection Cervarix: intramuscular injection	Randomized: 480 Group 1: 239 Group 2: 241	Mexico Endemic area 16 Nov 2016 to 25 Mar 2019	Healthy subjects 9–14 years	Completed Final CSR

CSR: clinical study report

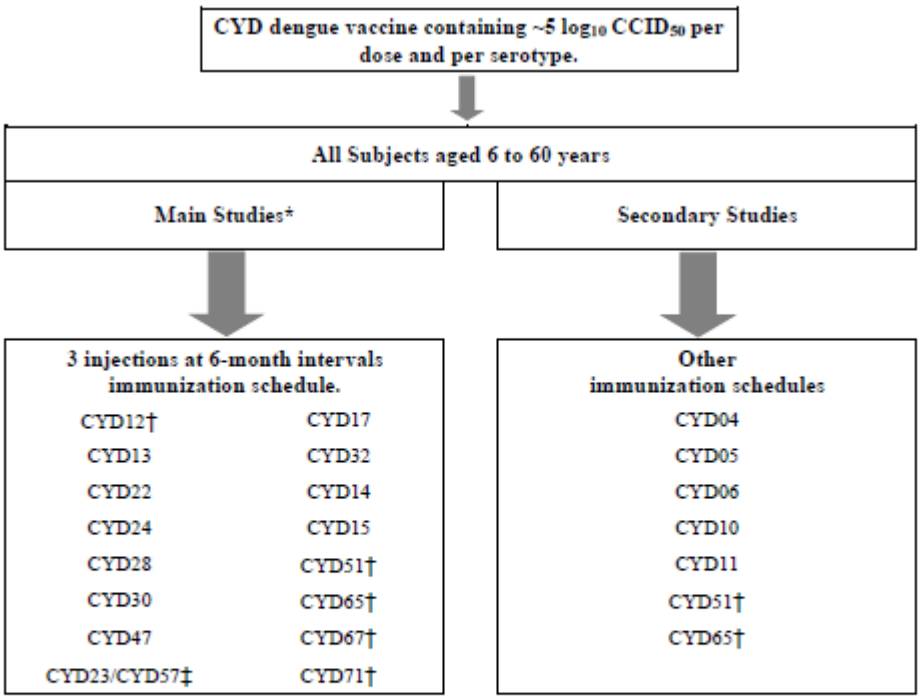
* FVFS – LVLS: First visit of the first subject – last visit of the last subject (LVLS includes last contact of subjects by telephone call)

Data from 17 studies using the final formulation and a 3-dose vaccination schedule at Day 0, Month 6 and Month 12 (D0/M6/M12) in subjects ≥6 years, referred to in the text as the "Main Studies", were part of the integrated/pooled analyses. Study CYD57, in which no vaccine was administered, was also part of the Main Studies for long-term safety follow-up objectives. Data from 7 studies using the final

formulation but a different vaccination schedule (referred to in the text as the "Secondary Studies") were used to support the Main Studies analyses in a limited number of tables.

For studies in which different vaccination schedules were evaluated, only applicable study groups were included in the Main Studies analysis.

Figure **4** and Figure 5 present the studies considered in the safety profile evaluation of the CYD dengue vaccine in subjects aged 6 to 60 years and 6 to 8 years, respectively.

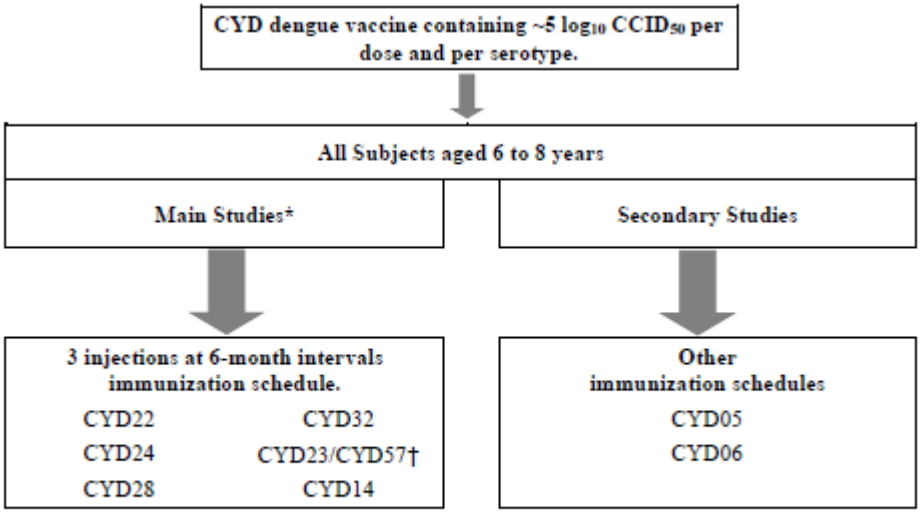


* Studies using the final formulation and a 3-dose vaccination schedule D0/M6/M12

† In studies that evaluated different schedules, only applicable study groups were included in the Main Studies analysis. See 5.3.5.3 Integrated Safety Analysis Report, Section 1.1.2 for additional information on studies contributing to the Main and Secondary Studies

‡ The long-term safety follow-up of subjects from CYD23 was carried out in CYD57, which is the 17th study that supports the safety analysis in this Application

Figure 4: Main and Secondary Studies Considered for the pooled/integrated analysis of safety in subjects aged 6 to 60 years



* Studies using the final formulation and a 3-dose vaccination schedule D0/M6/M12
† The long-term safety follow-up of subjects from CYD23 was carried out in CYD57

Figure 5: Main and Secondary Studies Considered for the pooled/integrated analysis of safety in subjects aged 6 to 8 years

In order to evaluate the long-term safety of the CYD dengue vaccine, long-term follow-up was implemented in several studies (i.e. CYD05, CYD22, CYD28, CYD23/57, CYD14, and CYD15) to assess SAEs, deaths, and hospitalized dengue cases.
Pre-defined solicited reactions (including injection site reactions collected for 7 days after each injection [pain, erythema, and swelling], and systemic reactions collected for 14 days after each injection [fever, headache, malaise, myalgia, and asthenia]) and all unsolicited reactions (up to 28 days) were collected for all participants following each injection in all studies except CYD23, CYD14, and CYD15, in which they were collected in a subset of subjects (i.e. the immunogenicity and reactogenicity subsets). All SAEs were collected up to at least 6 months after the last injection. In studies including a long-term follow-up, all SAEs were collected during the long-term follow-up, except in CYD05, CYD22, CYD57 and CYD28 in which a limited set of SAEs including related SAEs and hospitalized dengue cases was collected.

AESIs were also collected: AESIs including allergic reactions and anaphylaxis were collected within 7 days of each injection; viscerotropic and neurotropic events within 30 days; episodes of serious dengue disease throughout the entire studies.

Although the safety data have been presented in other age groups (6 to 60 years, 46 to 60 years, and 9 to 17 years), the CHMP assessment focussed on safety data in the new target population (6 to 8 years) and on data presented in the SmPC (from 6 to 17 years, and from 18-45 years). The data cut-off is the 19/03/2020.

Five studies included a long-term follow-up in subjects aged 6 to 8 years (CYD05, CYD22, CYD28, CYD23/57, and CYD14). SAEs were collected up to 48 months post-injection 3 in Phase II studies CYD22 and CYD28, and up to 60 months post-injection 3 in Phase I study CYD05, and Phase IIb/Phase III efficacy studies CYD23/57 and CYD14 (main studies).

In the pool of CYD14+CYD57, the mean duration of follow-up during the long-term safety follow-up of all the children aged 6 to 8 years was comparable in the CYD dengue vaccine Group (1608 days) and in the Placebo Group (1601 days), i.e. approximately 53 months, or 4.5 years. The median duration was also similar (1633 days in both groups). Individual study results were consistent with the pooled data. Similar results were observed in seropositive and seronegative subjects.

Patient exposure

A total of 30 145 subjects from 9 months through 60 years received at least 1 injection of the CYD dengue vaccine (~5 log10 CCID50 per dose and per serotype, regardless of the schedule) in 25 studies.

The number of subjects who received each comparator vaccine in the age categories 6 to 8 years, 9 to 17 years, 18 to 45 years, and 46 to 60 years are presented in table below:

Table 4: Overall extent of exposure, regardless of baseline dengue serostatus*, Subjects aged 6 to 60 years by Age Group - Safety Analysis Set (Table 1.8 of the Addendum to 2.7.4 Summary of Clinical Safety).

Age Groups:	CYD dengue vaccine (5555 formulation regardless of schedule)	CYD dengue vaccine (5555 formulation 3-dose schedule)	Placebo	Hepatitis A Vaccine	Influenza Vaccine	Japanese Encephalitis Vaccine	Meningococcal Vaccine	Pneumococcal Vaccine	Rabies Vaccine	Tdap Vaccine	Typhoid Vaccine	YF Vaccine
46-60 years												
At least 1 injection	408	293	147	0	0	0	0	0	0	0	0	0
At least 2 injections	332	278	83	-	-	-	-	-	-	-	-	-
3 injections	271	271	22	-	-	-	-	-	-	-	-	-
Total injections	1011	842	252	0	0	0	0	0	0	0	0	0
18-45 years												
At least 1 injection	2253	1492	665	0	164	30	10	0	0	0	16	155
At least 2 injections	1866	1360	256	-	160	-	-	-	-	-	-	-
3 injections	1547	1297	84	-	-	-	-	-	-	-	-	-
Total injections	5666	4149	1005	0	324	30	10	0	0	0	16	155
9-17 years												
At least 1 injection	20046	19719	9721	25	45	0	20	22	15	180	37	20
At least 2 injections	19420	19205	9305	25	44	-	-	-	-	-	-	-
3 injections	18775	18701	8829	-	-	-	-	-	-	-	-	-
Total injections	58241	57625	27855	50	89	0	20	22	15	180	37	20
6-8 years												
At least 1 injection	3262	3234	1598	28	0	0	10	25	26	0	16	4
At least 2 injections	3201	3174	1537	28	-	-	-	-	-	-	-	-
3 injections	3166	3148	1472	-	-	-	-	-	-	-	-	-
Total injections	9629	9556	4607	56	0	0	10	25	26	0	16	4
6-60 years												
At least 1 injection	25969	24738	12131	53	209	30	40	47	41	180	69	179
At least 2 injections	24819	24017	11181	53	204	-	-	-	-	-	-	-
3 injections	23759	23417	10407	-	-	-	-	-	-	-	-	-
Total injections	74547	72172	33719	106	413	30	40	47	41	180	69	179
2-5 years												
At least 1 injection	2525	2455	1174	23	0	0	20	43	9	0	31	12
At least 2 injections	2472	2408	1104	23	-	-	-	-	-	-	-	-
3 injections	2436	2397	1046	-	-	-	-	-	-	-	-	-
Total injections	7433	7260	3324	46	0	0	20	43	9	0	31	12

Only CYD dengue tetravalent formulations are considered for the CYD dengue columns
Tdap = tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine
CYD dengue vaccine 4.5 to 6 log10 CCID50 of serotypes 1, 2, 3 and 4
Contributing studies by age group:
46-60 years: CYD17 CYD65;
18-45 years: CYD04 CYD05 CYD06 CYD10 CYD11 CYD12 CYD17 CYD22 CYD28 CYD47 CYD51 CYD65;
9-17 years: CYD05 CYD06 CYD13 CYD14 CYD15 CYD22 CYD23 CYD24 CYD28 CYD30 CYD32 CYD65 CYD67 CYD71;
6-8 years: CYD05 CYD06 CYD14 CYD22 CYD23 CYD24 CYD28 CYD32;
6-60 years: CYD04 CYD05 CYD06 CYD10 CYD11 CYD12 CYD13 CYD14 CYD15 CYD17 CYD22 CYD23 CYD24 CYD28 CYD30 CYD32 CYD47 CYD51 CYD65 CYD67 CYD71;
2-5 years: CYD05 CYD06 CYD14 CYD22 CYD23 CYD24 CYD28 CYD32.

Safety data collected after a co-administrated injection will be excluded from further analyses

* Seropositive and seronegative subjects plus subjects with undetermined baseline dengue status or not assessed for baseline dengue status

Hepatitis A Vaccine = Havrix® pediatric formulation (Inactivated virus); Influenza Vaccine = Vaxigrip® (Split virion, inactivated); Japanese Encephalitis Vaccine = JE-VAX® (Inactivated virus); Meningococcal Vaccine = Menomune-A/C/Y/W-135® (Polysaccharide); Pneumococcal Vaccine = Pneumo23® (Polysaccharide); Rabies Vaccine = Verorab® (Inactivated virus); Tdap Vaccine = ADACEL® (Tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine adsorbed on aluminum phosphate); Typhoid Vaccine = Typhim Vi® (Polysaccharide); YF Vaccine = Stamaril Pasteur® (Live attenuated) or YF-VAX® (Live attenuated)

Source: Modified from 5.3.5.3 Integrated Safety Analysis Report, Table 3.5.0.1, 3.11.0.1, Table 3.12.0.1, Table 3.13.0.1, Table 3.14.0.1, and Table 3.18.0.1.

The CHMP noted that two thirds of the children aged 6 to 8 years received at least 1 injection in the 3-dose schedule of CYD dengue vaccine (5555 formulation) and on third were vaccinated with placebo. Only few children aged 6 to 8 years were vaccinated with other comparator vaccines (such as hepatitis A vaccine, meningococcal vaccine, pneumococcal vaccine, rabies vaccine, typhoid vaccine and yellow fever vaccine).

The safety analysis set (SafAS) for the 3-dose schedule included a total of 24 733 subjects aged 6 to 60 years who were randomized to the CYD dengue vaccine Group and received at least 1 injection of the

final formulation at the 3-dose schedule D0/M6/M12. It included the following number of subjects per age groups: 3233 children aged 6 to 8 years, 19 715 children / adolescents aged 9 to 17 years, 1492 adults aged 18 to 45 years, and 293 adults aged 46 to 60 years.

The Reactogenicity Subset for the 3-dose schedule included a total of 6219 subjects aged 6 to 60 years including: 768 children aged 6 to 8 years, 3666 children / adolescents aged 9 to 17 years, 1492 adults aged 18 to 45 years, and 293 adults aged 46 to 60 years.

For the evaluation of safety events after any injection of the 3-dose vaccination schedule D0/M6/M12, 3 groups were defined: CYD dengue vaccine Group (i.e. subjects who received at least 1 of the 3 planned CYD dengue vaccine injections), Placebo Group (i.e. subjects who received at least 1 injection of the 3 planned placebo injection and no CYD dengue vaccine or comparator vaccine), and Control Group (i.e. subjects who received at least 1 injection of either placebo or comparator vaccine and no CYD dengue vaccine).

The demographic characteristics were generally similar between the CYD dengue vaccine Group, Placebo Group, and Control Group regardless of the age group; however, differences in ethnic origin were a consequence of studies being conducted in different regions.

In the included 3233 children aged 6 to 8 years, the distribution between males and females was similar (table below). The mean age of subjects at enrolment for the combined regions was 7.0 years. There were no subjects aged 6 to 8 years from the non-endemic region.

In studies in the endemic AP region, among subjects with an available dengue serostatus (477 out of 3179 subjects), most were baseline seropositive (59.3%). In the endemic LatAm region, among subjects with an available dengue serostatus (52 out of 54 subjects), most were baseline seronegative (78.9%).

More details on the demographic characteristics for individual studies can be found in Integrated Safety Analysis Report, Tables Part 2,Table 3.11.0.9 and in the individual CSRs.

Table 5: Summary of subject demographics in subjects aged 6 to 8 years at first injection of the CYD dengue vaccine - SafAS Main Studies CYD Dengue Group

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

N: total number of subjects listed in the first three columns
M: number of subjects who provided ethnicity data
Percentages are based on the number of subjects with available data for the relevant category
Age is calculated at first vaccination regardless of what the subject received
The CYD dengue vaccine Group in Main Studies consists of subjects assigned to a 3-dose CYD dengue vaccine schedule [D0/M6/M12] and who received at least one dose of CYD dengue vaccine.

* Seropositive and seronegative subjects plus subjects with undetermined baseline dengue status or not assessed for baseline dengue status

Source: modified from 5.3.5.3 Integrated Safety Analysis Report, Table 3.11.0.9

The CHMP noted that 3233 children aged 6 to 8 years were included in the following studies: CYD05 (Philippines), CYD06 (Mexico), CYD22 (Vietnam), CYD24 (Peru), CYD28 (Singapore), CYD23 (Thailand), CYD32 (Malaysia), and CYD14 (Indonesia, Malaysia, Thailand, Philippines, Vietnam). The majority (3179 children) were from endemic Asia Pacific (AP), and all the subjects who provided ethnicity data were Asian (i.e. no ethnic origin data collected for the 54 children in the LatAm region).

Among subjects from the combined regions with an available dengue serostatus (529 out of 3233 subjects), 294 were baseline seropositive (55.6%).

Clinical safety in children aged 6 to 8 years

2.3.1.1. Adverse events

Safety Overview After Any Injection

In subjects aged 6 to 8 years, no immediate AEs were reported after any injection of the CYD dengue vaccine (table below).

Solicited injection site reactions were reported in slightly more than half of the subjects (56.1%) and few (0.4%) subjects experienced an injection site reaction of Grade 3 intensity. Solicited systemic reactions were reported in 67.5% of subjects and 5.7% of subjects experienced systemic reactions of Grade 3 intensity. Unsolicited non-serious ARs were reported in 3.1% of subjects and a single (0.1%) subject had one Grade 3 reaction (vomiting).

No anaphylactic reactions (SMQ algorithm), no serious allergic reactions, and a few non-serious allergic reactions (6 subjects, 0.8%) were reported. No subjects were identified with a potential post-vaccination dengue-like syndrome.

SAEs within 28 days after any injection occurred in 41 (1.3%) subjects and a single (< 0.1%) subject had 1 SAE assessed as related to the study vaccine by the Investigator (acute disseminated encephalomyelitis). Among the 181 subjects that reported SAEs between 28 days and 6 months post-injection, none experienced a related SAE.

There were no deaths within 6 months after any injection.

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

	CYD dengue vaccine			Placebo			Control		
Subjects experiencing at least one:	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)
REACTOGENICITY SUBSET									
Immediate unsolicited AE	0/768	0.0	(0.0; 0.5)	0/278	0.0	(0.0; 1.3)	0/370	0.0	(0.0; 1.0)
Immediate unsolicited AR	0/768	0.0	(0.0; 0.5)	0/278	0.0	(0.0; 1.3)	0/370	0.0	(0.0; 1.0)
Grade 3 immediate unsolicited AR	0/768	0.0	(0.0; 0.5)	0/278	0.0	(0.0; 1.3)	0/370	0.0	(0.0; 1.0)
Solicited reaction	586/766	76.5	(73.3; 79.5)	196/278	70.5	(64.8; 75.8)	261/370	70.5	(65.6; 75.1)
Grade 3 solicited reaction	45/766	5.9	(4.3; 7.8)	25/278	9.0	(5.9; 13.0)	31/370	8.4	(5.8; 11.7)
Solicited injection site reaction	430/766	56.1	(52.5; 59.7)	151/278	54.3	(48.3; 60.3)	207/370	55.9	(50.7; 61.1)
Grade 3 solicited injection site reaction	3/766	0.4	(0.1; 1.1)	1/278	0.4	(0.0; 2.0)	5/370	1.4	(0.4; 3.1)
Solicited systemic reaction	517/766	67.5	(64.0; 70.8)	169/278	60.8	(54.8; 66.6)	220/370	59.5	(54.3; 64.5)
Grade 3 solicited systemic reaction	44/766	5.7	(4.2; 7.6)	24/278	8.6	(5.6; 12.6)	26/370	7.0	(4.6; 10.1)

Unsolicited non-serious AE	336/768	43.8	(40.2; 47.3)	123/278	44.2	(38.3; 50.3)	169/370	45.7	(40.5; 50.9)
Unsolicited non-serious AR	24/768	3.1	(2.0; 4.6)	5/278	1.8	(0.6; 4.1)	6/370	1.6	(0.6; 3.5)
Grade 3 unsolicited non-serious AR	1/768	0.1	(0.0; 0.7)	0/278	0.0	(0.0; 1.3)	0/370	0.0	(0.0; 1.0)
Unsolicited non-serious injection site AR	12/768	1.6	(0.8; 2.7)	3/278	1.1	(0.2; 3.1)	3/370	0.8	(0.2; 2.4)
Grade 3 unsolicited non-serious injection site AR	0/768	0.0	(0.0; 0.5)	0/278	0.0	(0.0; 1.3)	0/370	0.0	(0.0; 1.0)
Unsolicited non-serious systemic AE	334/768	43.5	(39.9; 47.1)	123/278	44.2	(38.3; 50.3)	169/370	45.7	(40.5; 50.9)
Unsolicited non-serious systemic AR	14/768	1.8	(1.0; 3.0)	2/278	0.7	(0.1; 2.6)	3/370	0.8	(0.2; 2.4)
Grade 3 unsolicited non-serious systemic AR	1/768	0.1	(0.0; 0.7)	0/278	0.0	(0.0; 1.3)	0/370	0.0	(0.0; 1.0)
Anaphylactic reaction (SMQ)	0/768	0.0	(0.0; 0.5)	0/278	0.0	(0.0; 1.3)	0/370	0.0	(0.0; 1.0)
Non-serious allergic reaction (targeted list)	6/768	0.8	(0.3; 1.7)	1/278	0.4	(0.0; 2.0)	1/370	0.3	(0.0; 1.5)
Non-serious Grade 3 allergic reaction (targeted list)	0/768	0.0	(0.0; 0.5)	0/278	0.0	(0.0; 1.3)	0/370	0.0	(0.0; 1.0)
Post-vaccination dengue-like syndrome	0/768	0.0	(0.0; 0.5)	0/278	0.0	(0.0; 1.3)	0/370	0.0	(0.0; 1.0)
SAFETY ANALYSIS SET									
Discontinuation due to AE*	8/3233	0.2	(0.11; 0.49)	12/1505	0.8	(0.41; 1.39)	12/1597	0.8	(0.39; 1.31)
Serious allergic reaction (targeted list)	0/3233	0.0	(0.00; 0.11)	0/1505	0.0	(0.00; 0.24)	0/1597	0.0	(0.00; 0.23)
SAE <=28 days	41/3233	1.3	(0.91; 1.72)	28/1505	1.9	(1.24; 2.68)	29/1597	1.8	(1.22; 2.60)
SAE >28 days to 6 months post dose	181/3233	5.6	(4.83; 6.45)	105/1505	7.0	(5.74; 8.38)	110/1597	6.9	(5.69; 8.24)
Related SAE <=28 days	1/3233	<0.1	(0.00; 0.17)	2/1505	0.1	(0.02; 0.48)	2/1597	0.1	(0.02; 0.45)
Related SAE >28 days to 6 months post dose	0/3233	0.0	(0.00; 0.11)	0/1505	0.0	(0.00; 0.24)	0/1597	0.0	(0.00; 0.23)
Neurological disorder SAE <=30 days	1/3233	<0.1	(0.00; 0.17)	3/1505	0.2	(0.04; 0.58)	3/1597	0.2	(0.04; 0.55)
Neurological disorder SAE >30 days to 6 months	4/3233	0.1	(0.03; 0.32)	4/1505	0.3	(0.07; 0.68)	4/1597	0.3	(0.07; 0.64)
Death within 6 months	0/3233	0.0	(0.00; 0.11)	5/1505	0.3	(0.11; 0.77)	5/1597	0.3	(0.10; 0.73)
Related death within 6 months	0/3233	0.0	(0.00; 0.11)	0/1505	0.0	(0.00; 0.24)	0/1597	0.0	(0.00; 0.23)

n: number of subjects experiencing the endpoint

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

CYD dengue vaccine 5 = 1 log10 CCID50 of serotypes 1, 2, 3 and 4

Main studies applied a D0/M6/M12 vaccine schedule

* Identified in the termination form as SAE or other AE

Contributing studies: CYD14 CYD22 CYD23 CYD24 CYD28 CYD32

Unsolicited non-serious AEs and ARs that occurred within the 28 days post-injection visit's time window (+14 days in most studies) were also included in the Safety Overview tables to provide a more comprehensive overview

Source: modified from 5.3.5.3 Integrated Safety Analysis Report, Table 3.11.1.3.

The CHMP considered that, overall, in children from 6 to 8 years regardless of baseline dengue serostatus (after any 3 doses), the safety profiles of the CYD dengue vaccine were similar to the placebo and control groups.

However, in the reactogenicity subset, slightly higher percentages were observed for:

- solicited reactions (76.5% vs. 70.5% vs. 70.5%, respectively), solicited systemic reactions (67.5% vs. 60.8% vs. 59.5%)

- unsolicited non-serious AR (3.1% vs. 1.8% vs. 1.6%), unsolicited non-serious injection site AR (1.6% vs. 1.1% vs. 0.8%), unsolicited non-serious systemic AR (1.8% vs. 0.7% vs. 0.8%)

- non-serious allergic reactions – targeted list (0.8% vs. 0.4% vs. 0.3%)

Nevertheless, slightly lower or similar percentage were observed for:

- grade 3 solicited reactions (5.9% vs. 9% vs. 8.4%, respectively),

- solicited injection site reaction, all (56.1% vs. 54.3% vs. 55.9%) and grade 3

- grade 3 solicited systemic reactions (5.7% vs. 8.6% vs. 7%)

- unsolicited non-serious AE (43.8% vs. 44.2% vs. 45.7%), grade 3 unsolicited non-serious AR (0.1% - 1 case: vomiting- vs. 0% vs. 0%), no grade 3 unsolicited non-serious injection site AR, grade 3 unsolicited non-serious systemic AR (0.1% vs. 0% vs. 0%)

- no grade 3 non-serious allergic reactions – targeted list

There were no immediate unsolicited AE/AR, no anaphylactic reaction (SMQ) and no post-vaccination dengue-like syndrome in the 3 groups.

In the safety analysis set, slightly lower or similar percentages were observed for: discontinuation due to AE (0.2% vs. 0.8% vs. 0.8%), SAE ≤ 28 days (1.3% vs. 1.9% vs. 1.8%), SAE > 28 days to 6 months post dose (5.6% vs. 7% vs. 6.9%), related SAE ≤ 28 days (<0.1% - 1 case: acute disseminated encephalomyelitis - vs. 0.1% vs. 0.1%), neurological disorder SAE ≤ 30 days (<0.1% vs. 0.2% vs. 0.2%), neurological disorder SAE > 30 days to 6 months (0.1% vs. 0.3% vs. 0.3%), and death within 6 months (0% vs. 0.3% vs. 0.3%).

There were no serious allergic reactions (targeted list), no related SAE > 28 days to 6 months post dose, and no related death within 6 months in the 3 groups.

Table 7: Safety overview after any of 3 doses of CYD dengue vaccine or Placebo or Control, baseline dengue seropositive subjects - Subjects 6 to 8 years - SafAS Main Studies Pooled

	CYD dengue vaccine			Placebo			Control		
Subjects experiencing at least one:	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)
REACTOGENICITY SUBSET									
Immediate unsolicited AE	0/294	0.0	(0.0; 1.2)	0/110	0.0	(0.0; 3.3)	0/152	0.0	(0.0; 2.4)
Immediate unsolicited AR	0/294	0.0	(0.0; 1.2)	0/110	0.0	(0.0; 3.3)	0/152	0.0	(0.0; 2.4)
Grade 3 immediate unsolicited AR	0/294	0.0	(0.0; 1.2)	0/110	0.0	(0.0; 3.3)	0/152	0.0	(0.0; 2.4)
Solicited reaction	197/293	67.2	(61.5; 72.6)	65/110	59.1	(49.3; 68.4)	94/152	61.8	(53.6; 69.6)
Grade 3 solicited reaction	20/293	6.8	(4.2; 10.3)	5/110	4.5	(1.5; 10.3)	9/152	5.9	(2.7; 10.9)
Solicited injection site reaction	147/293	50.2	(44.3; 56.0)	45/110	40.9	(31.6; 50.7)	70/152	46.1	(37.9; 54.3)
Grade 3 solicited injection site reaction	1/293	0.3	(0.0; 1.9)	0/110	0.0	(0.0; 3.3)	2/152	1.3	(0.2; 4.7)
Solicited systemic reaction	167/293	57.0	(51.1; 62.7)	57/110	51.8	(42.1; 61.4)	81/152	53.3	(45.0; 61.4)
Grade 3 solicited systemic reaction	20/293	6.8	(4.2; 10.3)	5/110	4.5	(1.5; 10.3)	7/152	4.6	(1.9; 9.3)
Unsolicited non-serious AE	110/294	37.4	(31.9; 43.2)	45/110	40.9	(31.6; 50.7)	69/152	45.4	(37.3; 53.7)
Unsolicited non-serious AR	5/294	1.7	(0.6; 3.9)	3/110	2.7	(0.6; 7.8)	3/152	2.0	(0.4; 5.7)
Grade 3 unsolicited non-serious AR	0/294	0.0	(0.0; 1.2)	0/110	0.0	(0.0; 3.3)	0/152	0.0	(0.0; 2.4)
Unsolicited non-serious injection site AR	2/294	0.7	(0.1; 2.4)	1/110	0.9	(0.0; 5.0)	1/152	0.7	(0.0; 3.6)
Grade 3 unsolicited non-serious injection site AR	0/294	0.0	(0.0; 1.2)	0/110	0.0	(0.0; 3.3)	0/152	0.0	(0.0; 2.4)
Unsolicited non-serious systemic AE	109/294	37.1	(31.5; 42.9)	45/110	40.9	(31.6; 50.7)	69/152	45.4	(37.3; 53.7)
Unsolicited non-serious systemic AR	3/294	1.0	(0.2; 3.0)	2/110	1.8	(0.2; 6.4)	2/152	1.3	(0.2; 4.7)
Grade 3 unsolicited non-serious systemic AR	0/294	0.0	(0.0; 1.2)	0/110	0.0	(0.0; 3.3)	0/152	0.0	(0.0; 2.4)
Anaphylactic reaction (SMQ)	0/294	0.0	(0.0; 1.2)	0/110	0.0	(0.0; 3.3)	0/152	0.0	(0.0; 2.4)
Non-serious allergic reaction (targeted list)	3/294	1.0	(0.2; 3.0)	1/110	0.9	(0.0; 5.0)	1/152	0.7	(0.0; 3.6)
Non-serious Grade 3 allergic reaction (targeted list)	0/294	0.0	(0.0; 1.2)	0/110	0.0	(0.0; 3.3)	0/152	0.0	(0.0; 2.4)
Post-vaccination dengue-like syndrome	0/294	0.0	(0.0; 1.2)	0/110	0.0	(0.0; 3.3)	0/152	0.0	(0.0; 2.4)
SAFETY ANALYSIS SET									
Discontinuation due to AE*	1/294	0.3	(0.01; 1.88)	1/110	0.9	(0.02; 4.96)	1/152	0.7	(0.02; 3.61)
Serious allergic reaction (targeted list)	0/294	0.0	(0.00; 1.25)	0/110	0.0	(0.00; 3.30)	0/152	0.0	(0.00; 2.40)
SAE <=28 days	4/294	1.4	(0.37; 3.45)	2/110	1.8	(0.22; 6.41)	3/152	2.0	(0.41; 5.66)
SAE >28 days to 6 months post dose	17/294	5.8	(3.40; 9.10)	6/110	5.5	(2.03; 11.49)	8/152	5.3	(2.30; 10.11)
Related SAE <=28 days	0/294	0.0	(0.00; 1.25)	0/110	0.0	(0.00; 3.30)	0/152	0.0	(0.00; 2.40)
Related SAE >28 days to 6 months post dose	0/294	0.0	(0.00; 1.25)	0/110	0.0	(0.00; 3.30)	0/152	0.0	(0.00; 2.40)
Neurological disorder SAE <=30 days	0/294	0.0	(0.00; 1.25)	0/110	0.0	(0.00; 3.30)	0/152	0.0	(0.00; 2.40)
Neurological disorder SAE >30 days to 6 months	0/294	0.0	(0.00; 1.25)	0/110	0.0	(0.00; 3.30)	0/152	0.0	(0.00; 2.40)
Death within 6 months	0/294	0.0	(0.00; 1.25)	0/110	0.0	(0.00; 3.30)	0/152	0.0	(0.00; 2.40)
Related death within 6 months	0/294	0.0	(0.00; 1.25)	0/110	0.0	(0.00; 3.30)	0/152	0.0	(0.00; 2.40)

n: number of subjects experiencing the endpoint

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

CYD dengue vaccine 5 ± 1 log10 CCID50 of serotypes 1, 2, 3 and 4

Main studies applied a D0/M6/M12 vaccine schedule

* Identified in the termination form as SAE or other AE

Contributing studies: CYD14 CYD22 CYD23 CYD24 CYD28 CYD32

Unsolicited non-serious AEs and ARs that occurred within the 28 days post-injection visit's time window (+14 days in most studies) were also included in the Safety Overview tables to provide a more comprehensive overview

Source: modified from 5.3.5.3 Integrated Safety Analysis Report, Table 3.11.1.3.

The CHMP considered that, overall, the safety profile in seropostive subjects aged 6 to 8 years was similar to the one in subjects aged 6 to 8 years regardless of the baseline dengue serostatus.

The trend toward a slightly higher incidence of solicited systemic reactions in the CYD dengue vaccine Group was also observed in baseline seropositive subjects (57.0% vs. 51.8% in PBO vs. 53.3% in control

group). A slightly higher incidence was also observed for grade 3 solicited systemic reactions (6.8% vs. 4.5% vs. 4.6%, respectively). Moreover, in baseline dengue seropositive subjects, there was a trend toward a higher incidence of solicited injection site reactions in the CYD dengue vaccine Group (50.2% vs. 40.9% in PBO vs. 46.1% in control group).

Overall, in baseline seropositive subjects, there were no other major differences in the incidence reactogenicity and safety events between the CYD dengue vaccine Group and the Placebo and Control Groups.

Solicited injection site reactions and solicited systemic reactions were observed at a lower frequencies in dengue seropositive subjects (50.2% and 57%, respectively) compared to all subjects regardless of baseline dengue serostatus (56.1% and 67.5%, respectively). Unsolicited non-serious AE (mainly systemic) were also observed at a lower frequencies in dengue seropositive subjects (37.4%) compared to all subjects regardless of baseline dengue serostatus (43.8%).

Safety Overview After each Injection of the CYD dengue vaccine

Table 8: Safety overview after each CYD dengue vaccine dose, regardless of baseline dengue serostatus - Subjects 6 to 8 years - SafAS Main Studies Pooled

	Dose 1			Dose 2			Dose 3		
Subjects experiencing at least one:	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)
REACTOGENICITY SUBSET									
Immediate unsolicited AE	0/768	0.0	(0.0; 0.5)	0/753	0.0	(0.0; 0.5)	0/744	0.0	(0.0; 0.5)
Immediate unsolicited AR	0/768	0.0	(0.0; 0.5)	0/753	0.0	(0.0; 0.5)	0/744	0.0	(0.0; 0.5)
Grade 3 immediate unsolicited AR	0/768	0.0	(0.0; 0.5)	0/753	0.0	(0.0; 0.5)	0/744	0.0	(0.0; 0.5)
Solicited reaction	465/766	60.7	(57.1; 64.2)	382/751	50.9	(47.2; 54.5)	335/744	45.0	(41.4; 48.7)
Grade 3 solicited reaction	20/766	2.6	(1.6; 4.0)	19/751	2.5	(1.5; 3.9)	11/744	1.5	(0.7; 2.6)
Solicited injection site reaction	275/765	35.9	(32.5; 39.5)	256/751	34.1	(30.7; 37.6)	238/744	32.0	(28.6; 35.5)
Grade 3 solicited injection site reaction	0/765	0.0	(0.0; 0.5)	1/751	0.1	(0.0; 0.7)	2/744	0.3	(0.0; 1.0)
Solicited systemic reaction	371/766	48.4	(44.8; 52.0)	302/751	40.2	(36.7; 43.8)	247/744	33.2	(29.8; 36.7)
Grade 3 solicited systemic reaction	20/766	2.6	(1.6; 4.0)	19/751	2.5	(1.5; 3.9)	10/744	1.3	(0.6; 2.5)
Unsolicited non-serious AE	195/768	25.4	(22.3; 28.6)	158/753	21.0	(18.1; 24.1)	120/744	16.1	(13.6; 19.0)
Unsolicited non-serious AR	15/768	2.0	(1.1; 3.2)	8/753	1.1	(0.5; 2.1)	4/744	0.5	(0.1; 1.4)
Grade 3 unsolicited non-serious AR	0/768	0.0	(0.0; 0.5)	0/753	0.0	(0.0; 0.5)	1/744	0.1	(0.0; 0.7)
Unsolicited non-serious injection site AR	8/768	1.0	(0.5; 2.0)	2/753	0.3	(0.0; 1.0)	3/744	0.4	(0.1; 1.2)
Grade 3 unsolicited non-serious injection site AR	0/768	0.0	(0.0; 0.5)	0/753	0.0	(0.0; 0.5)	0/744	0.0	(0.0; 0.5)
Unsolicited non-serious systemic AE	193/768	25.1	(22.1; 28.4)	156/753	20.7	(17.9; 23.8)	117/744	15.7	(13.2; 18.5)
Unsolicited non-serious systemic AR	8/768	1.0	(0.5; 2.0)	6/753	0.8	(0.3; 1.7)	1/744	0.1	(0.0; 0.7)
Grade 3 unsolicited non-serious systemic AR	0/768	0.0	(0.0; 0.5)	0/753	0.0	(0.0; 0.5)	1/744	0.1	(0.0; 0.7)
Anaphylactic reaction (SMQ)	0/768	0.0	(0.0; 0.5)	0/753	0.0	(0.0; 0.5)	0/744	0.0	(0.0; 0.5)
Non-serious allergic reaction (targeted list)	3/768	0.4	(0.1; 1.1)	1/753	0.1	(0.0; 0.7)	2/744	0.3	(0.0; 1.0)
Non-serious Grade 3 allergic reaction (targeted list)	0/768	0.0	(0.0; 0.5)	0/753	0.0	(0.0; 0.5)	0/744	0.0	(0.0; 0.5)
Post-vaccination dengue-like syndrome	0/768	0.0	(0.0; 0.5)	0/753	0.0	(0.0; 0.5)	0/744	0.0	(0.0; 0.5)
SAFETY ANALYSIS SET									
Discontinuation due to AE*	3/3234	<0.1	(0.02; 0.27)	4/3174	0.1	(0.03; 0.32)	1/3148	<0.1	(0.00; 0.18)
Serious allergic reaction (targeted list)	0/3234	0.0	(0.00; 0.11)	0/3174	0.0	(0.00; 0.12)	0/3148	0.0	(0.00; 0.12)
SAE <=28 days	22/3234	0.7	(0.43; 1.03)	13/3174	0.4	(0.22; 0.70)	8/3148	0.3	(0.11; 0.50)
SAE >28 days to 6 months post dose	62/3234	1.9	(1.47; 2.45)	74/3174	2.3	(1.84; 2.92)	55/3148	1.7	(1.32; 2.27)
Related SAE <=28 days	1/3234	<0.1	(0.00; 0.17)	0/3174	0.0	(0.00; 0.12)	0/3148	0.0	(0.00; 0.12)
Related SAE >28 days to 6 months post dose	0/3234	0.0	(0.00; 0.11)	0/3174	0.0	(0.00; 0.12)	0/3148	0.0	(0.00; 0.12)

Neurological disorder SAE <=30 days	1/3234	<0.1	(0.00; 0.17)	0/3174	0.0	(0.00; 0.12)	0/3148	0.0	(0.00; 0.12)
Neurological disorder SAE >30 days to 6 months	0/3234	0.0	(0.00; 0.11)	3/3174	<0.1	(0.02; 0.28)	1/3148	<0.1	(0.00; 0.18)
Death within 6 months	0/3234	0.0	(0.00; 0.11)	0/3174	0.0	(0.00; 0.12)	0/3148	0.0	(0.00; 0.12)
Related death within 6 months	0/3234	0.0	(0.00; 0.11)	0/3174	0.0	(0.00; 0.12)	0/3148	0.0	(0.00; 0.12)

n: number of subjects experiencing the endpoint

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

CYD dengue vaccine 5 ± 1 log10 CCID50 of serotypes 1, 2, 3 and 4

Main studies applied a D0/M6/M12 vaccine schedule

* Identified in the termination form as SAE or other AE

Contributing studies: CYD14 CYD22 CYD23 CYD24 CYD28 CYD32

Unsolicited non-serious AEs and ARs that occurred within the 28 days post-injection visit's time window (+14 days in most studies) were also included in the Safety Overview tables to provide a more comprehensive overview

Source: modified from 5.3.5.3 Integrated Safety Analysis Report, Table 3.11.1.1.

3.11.1.1 : Safety overview after each CYD dengue vaccine dose - Subjects 6-8 - SafAS Main Studies Pooled

Table 9: Safety overview after each CYD dengue vaccine dose, baseline dengue seropositive subjects - Subjects 6 to 8 years - SafAS Main Studies Pooled

	Dose 1			Dose 2			Dose 3		
Subjects experiencing at least one:	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)
REACTOGENICITY SUBSET									
Immediate unsolicited AE	0/294	0.0	(0.0; 1.2)	0/289	0.0	(0.0; 1.3)	0/285	0.0	(0.0; 1.3)
Immediate unsolicited AR	0/294	0.0	(0.0; 1.2)	0/289	0.0	(0.0; 1.3)	0/285	0.0	(0.0; 1.3)
Grade 3 immediate unsolicited AR	0/294	0.0	(0.0; 1.2)	0/289	0.0	(0.0; 1.3)	0/285	0.0	(0.0; 1.3)
Solicited reaction	151/293	51.5	(45.7; 57.4)	118/289	40.8	(35.1; 46.7)	109/285	38.2	(32.6; 44.2)
Grade 3 solicited reaction	7/293	2.4	(1.0; 4.9)	10/289	3.5	(1.7; 6.3)	4/285	1.4	(0.4; 3.6)
Solicited injection site reaction	91/292	31.2	(25.9; 36.8)	80/289	27.7	(22.6; 33.2)	78/285	27.4	(22.3; 32.9)
Grade 3 solicited injection site reaction	0/292	0.0	(0.0; 1.3)	1/289	0.3	(0.0; 1.9)	0/285	0.0	(0.0; 1.3)
Solicited systemic reaction	118/293	40.3	(34.6; 46.1)	86/289	29.8	(24.5; 35.4)	76/285	26.7	(21.6; 32.2)
Grade 3 solicited systemic reaction	7/293	2.4	(1.0; 4.9)	10/289	3.5	(1.7; 6.3)	4/285	1.4	(0.4; 3.6)
Unsolicited non-serious AE	64/294	21.8	(17.2; 26.9)	45/289	15.6	(11.6; 20.3)	37/285	13.0	(9.3; 17.4)
Unsolicited non-serious AR	3/294	1.0	(0.2; 3.0)	3/289	1.0	(0.2; 3.0)	0/285	0.0	(0.0; 1.3)
Grade 3 unsolicited non-serious AR	0/294	0.0	(0.0; 1.2)	0/289	0.0	(0.0; 1.3)	0/285	0.0	(0.0; 1.3)
Unsolicited non-serious injection site AR	2/294	0.7	(0.1; 2.4)	1/289	0.3	(0.0; 1.9)	0/285	0.0	(0.0; 1.3)
Grade 3 unsolicited non-serious injection site AR	0/294	0.0	(0.0; 1.2)	0/289	0.0	(0.0; 1.3)	0/285	0.0	(0.0; 1.3)
Unsolicited non-serious systemic AE	63/294	21.4	(16.9; 26.6)	44/289	15.2	(11.3; 19.9)	37/285	13.0	(9.3; 17.4)
Unsolicited non-serious systemic AR	1/294	0.3	(0.0; 1.9)	2/289	0.7	(0.1; 2.5)	0/285	0.0	(0.0; 1.3)
Grade 3 unsolicited non-serious systemic AR	0/294	0.0	(0.0; 1.2)	0/289	0.0	(0.0; 1.3)	0/285	0.0	(0.0; 1.3)
Anaphylactic reaction (SMQ)	0/294	0.0	(0.0; 1.2)	0/289	0.0	(0.0; 1.3)	0/285	0.0	(0.0; 1.3)
Non-serious allergic reaction (targeted list)	1/294	0.3	(0.0; 1.9)	1/289	0.3	(0.0; 1.9)	1/285	0.4	(0.0; 1.9)
Non-serious Grade 3 allergic reaction (targeted list)	0/294	0.0	(0.0; 1.2)	0/289	0.0	(0.0; 1.3)	0/285	0.0	(0.0; 1.3)
Post vaccination dengue-like syndrome	0/294	0.0	(0.0; 1.2)	0/289	0.0	(0.0; 1.3)	0/285	0.0	(0.0; 1.3)
SAFETY ANALYSIS SET									
Discontinuation due to AE*	0/294	0.0	(0.00; 1.25)	1/289	0.3	(0.01; 1.91)	0/285	0.0	(0.00; 1.29)
Serious allergic reaction (targeted list)	0/294	0.0	(0.00; 1.25)	0/289	0.0	(0.00; 1.27)	0/285	0.0	(0.00; 1.29)
SAE <=28 days	3/294	1.0	(0.21; 2.95)	0/289	0.0	(0.00; 1.27)	1/285	0.4	(0.01; 1.94)
SAE >28 days to 6 months post dose	9/294	3.1	(1.41; 5.73)	4/289	1.4	(0.38; 3.51)	4/285	1.4	(0.38; 3.55)
Related SAE <=28 days	0/294	0.0	(0.00; 1.25)	0/289	0.0	(0.00; 1.27)	0/285	0.0	(0.00; 1.29)
Related SAE >28 days to 6 months post dose	0/294	0.0	(0.00; 1.25)	0/289	0.0	(0.00; 1.27)	0/285	0.0	(0.00; 1.29)
Neurological disorder SAE <=30 days	0/294	0.0	(0.00; 1.25)	0/289	0.0	(0.00; 1.27)	0/285	0.0	(0.00; 1.29)
Neurological disorder SAE >30 days to 6 months	0/294	0.0	(0.00; 1.25)	0/289	0.0	(0.00; 1.27)	0/285	0.0	(0.00; 1.29)
Death within 6 months	0/294	0.0	(0.00; 1.25)	0/289	0.0	(0.00; 1.27)	0/285	0.0	(0.00; 1.29)
Related death within 6 months	0/294	0.0	(0.00; 1.25)	0/289	0.0	(0.00; 1.27)	0/285	0.0	(0.00; 1.29)

n: number of subjects experiencing the endpoint.

M: number of subjects with available data for the relevant endpoint
CYD dengue vaccine 5 ± 1 log10 CCID50 of serotypes 1, 2, 3 and 4.
Main studies applied a D0/M6/M12 vaccine schedule
* Identified in the termination form as SAE or other AE
Contributing studies: CYD14 CYD22 CYD23 CYD24 CYD28 CYD32

Unsolicited non-serious AEs and ARs that occurred within the 28 days post-injection visit's time window (+14 days in most studies) were also included in the Safety Overview tables to provide a more comprehensive overview

Source: modified from 5.3.5.3 Integrated Safety Analysis Report, Table 3.11.1.1 (see "Integrated Summary of Safety [ISS] - Tables – Part 2" submitted in eCTD sequence 0029).

The CHMP noted that, regardless of baseline dengue serostatus, the incidence of most parameters tended to decrease with each subsequent injection, most notably solicited injection reactions (35.9%, 34.1%, and 32.0%), solicited systemic reactions (48.4%, 40.2%, and 33.2%), unsolicited non-serious AEs (25.4%, 21.0%, and 16.1%) and unsolicited non-serious systemic AE (25.1%, 20.7%, and 15.7%).

Immediate AEs and ARs, anaphylactic reactions (SMQ), non-serious and serious potential allergic reactions, post-vaccination dengue-like syndrome, discontinuation due to AEs, SAEs within 28 days, and neurological disorder SAEs were reported at low frequencies after each injection (i.e. between 0.0% and 0.7%).

Similarly, in baseline seropositive subjects, the incidence of most parameters tended to decrease with each subsequent injection, most notably solicited injection reactions (31.2%, 27.7%, and 27.4%), solicited systemic reactions (40.3%, 29.8%, and 26.7%), unsolicited non-serious AEs (21.8%, 15.6% and 13%) and unsolicited non-serious systemic AE (21.4%, 15.2%, and 13%).

Immediate AEs and ARs, anaphylactic reactions (SMQ), non-serious and serious potential allergic reactions, post-vaccination dengue-like syndrome, discontinuation due to AEs, SAEs within 28 days, and neurological disorder SAEs were reported at low frequencies after each injection (i.e. between 0.0% and 1%).

The comparison of the safety profile in the main studies (i.e. studies in which the CYD dengue vaccine was administered according to the final schedule) to the safety profile in the Secondary Studies (i.e. studies using other vaccination schedules than the final 3-dose schedule) will not be discussed in this report as the number of subjects in the Secondary Studies was very low compared to that in the Main Studies (20 versus 768 subjects).

Similarly, the comparison will not be done with the safety profile after a first injection of comparator vaccines (hepatitis A, meningococcal, pneumococcal, rabies, typhoid, YF), as among studies in which comparator vaccines were administered, the ones with the highest number of subjects receiving a comparator vaccine were CYD23 (26 subjects; rabies), CYD24 (25 subjects; pneumococcal), and CYD28 (28 subjects; hepatitis A).

Immediate adverse events

In subjects aged 6 to 8 years, no immediate unsolicited AEs were reported in any of the 3 treatment groups.

Solicited local reaction

After Any Injection

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

Table 10: Solicited injection site reactions after any of 3 doses of CYD dengue vaccine or Placebo or Control, regardless of baseline dengue serostatus, by maximum intensity during the solicited period - Subjects 6 to 8 years - RS Main Studies Pooled

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

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

Source: modified from 5.3.5.3 Integrated Safety Analysis Report, Table 3.11.1.15.

The CHMP noted that, in children from 6 to 8 years regardless of baseline dengue serostatus (after any 3 doses), solicited injection site reactions were reported with similar frequencies in the CYD dengue vaccine (56.1%), Placebo (54.3%), and Control Groups (55.9%). Similarly, the 3 types of solicited injection site reactions were reported with similar frequencies in each group. In each of them, pain (51.4%, 48.9%, and 51.4% of subjects, respectively) was the most frequently reported injection site reactions, followed by erythema (21.7%, 24.1%, and 22.7%, respectively), and swelling (16.2%, 16.5%, 16.5%, respectively).

Most solicited injection site reactions were Grade 1, occurred within 3 days after injection and had between 1 and 3 days of occurrence.

In CYD dengue vaccine group, a total of 3 (0.4%) subjects experienced 4 Grade 3 injection site reactions: a subject reported Grade 3 injection site pain after the second injection, another subject reported Grade 3 injection site pain after the third injection, and the last subject reported Grade 3 injection site pain and swelling after the third injection.

As seen before, in baseline seropositive subjects, there was a trend toward a higher incidence of solicited injection site reactions in the CYD dengue vaccine Group (50.2% vs. 40.9% in PBO vs. 46.1% in control group). Pain in particular has a higher incidence in the CYD dengue vaccine group (46.1%) compared to PBO (37.3%) and control group (42.8%). The 2 other types of solicited injection site reactions were reported with similar frequencies in each group: erythema (14.3%, 14.5%, and 15.8%, respectively), and swelling (12.7%, 9.1%, 11.2%, respectively).

In dengue seropositive subjects, all solicited injection site reactions, pain, erythema and swelling were observed at a lower frequencies compared to all subjects regardless of baseline dengue serostatus.

After each Injection of the CYD dengue vaccine

The incidence of solicited injection site reactions within 7 days after each CYD dengue vaccine dose is presented in table below.

Table 11: Solicited injection site reactions after each CYD dengue vaccine dose, regardless of baseline dengue serostatus, by maximum intensity during the solicited period – Subjects 6 to 8 years - RS Main Studies Pooled

		Dose 1			Dose 2			Dose 3		
Subjects experiencing at least one:	Maximum intensity	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)
Pain		237/765	31.0	(27.7; 34.4)	233/751	31.0	(27.7; 34.5)	211/744	28.4	(25.1; 31.7)
	Grade 1	227/765	29.7	(26.5; 33.0)	221/751	29.4	(26.2; 32.8)	201/744	27.0	(23.9; 30.4)
	Grade 2	10/765	1.3	(0.6; 2.4)	11/751	1.5	(0.7; 2.6)	8/744	1.1	(0.5; 2.1)
	Grade 3	0/765	0.0	(0.0; 0.5)	1/751	0.1	(0.0; 0.7)	2/744	0.3	(0.0; 1.0)
Erythema		76/765	9.9	(7.9; 12.3)	76/751	10.1	(8.1; 12.5)	75/744	10.1	(8.0; 12.5)
	Grade 1	74/765	9.7	(7.7; 12.0)	75/751	10.0	(7.9; 12.4)	75/744	10.1	(8.0; 12.5)
	Grade 2	2/765	0.3	(0.0; 0.9)	1/751	0.1	(0.0; 0.7)	0/744	0.0	(0.0; 0.5)
	Grade 3	0/765	0.0	(0.0; 0.5)	0/751	0.0	(0.0; 0.5)	0/744	0.0	(0.0; 0.5)
Swelling		60/764	7.9	(6.0; 10.0)	51/751	6.8	(5.1; 8.8)	59/744	7.9	(6.1; 10.1)
	Grade 1	57/764	7.5	(5.7; 9.6)	51/751	6.8	(5.1; 8.8)	57/744	7.7	(5.9; 9.8)
	Grade 2	3/764	0.4	(0.1; 1.1)	0/751	0.0	(0.0; 0.5)	1/744	0.1	(0.0; 0.7)
	Grade 3	0/764	0.0	(0.0; 0.5)	0/751	0.0	(0.0; 0.5)	1/744	0.1	(0.0; 0.7)

n: number of subjects experiencing the endpoint
M: number of subjects with available data for the relevant endpoint
CYD dengue vaccine 5 ± 1 log10 CCID50 of serotypes 1, 2, 3 and 4
Main studies applied a D0/M6/M12 vaccine schedule
Contributing studies: CYD14 CYD22 CYD23 CYD24 CYD28 CYD32

Source: modified from 5.3.5.3 Integrated Safety Analysis Report, Table 3.11.1.14.

The CHMP noted that, overall, in children from 6 to 8 years regardless of baseline dengue serostatus, the incidence of solicited injection site reactions tended to decrease very slightly after each injection (35.9%, 34.1%, and 32% after the first, second, and third dose, respectively). However, the incidence of each solicited injection site reactions tended to be similar after each injection: pain (31%, 31%, and 28.4% of subjects after the first, second and third dose, respectively), erythema (9.9%, 10.1%, 10.1%, respectively), and swelling (7.9%, 6.8%, and 7.9%, respectively).

In baseline seropositive subjects, the incidence of solicited injection site reactions tended to decrease very slightly after each injection (31.2%, 27.7%, and 27.4% after the first, second, and third dose, respectively), and also the incidence of each solicited injection site reactions: pain (27.4%, 25.3%, and 25.3% of subjects after the first, second and third dose, respectively), erythema (7.2%, 6.9%, 4.9%, respectively), and swelling (7.2%, 4.8%, and 4.2%, respectively.

Solicited systemic reaction

After Any Injection

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

Table 12: Solicited systemic reactions after any of 3 doses of CYD dengue vaccine or Placebo or Control, regardless of baseline dengue serostatus, by maximum intensity during the solicited period - Subjects 6 to 8 years - RS Main Studies Pooled

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

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

Source: Reproduced from 5.3.5.3 Integrated Safety Analysis Report, Table 3.11.1.22.

As previously observed, the CHMP noted that in children from 6 to 8 years regardless of baseline dengue serostatus (after any 3 doses), there was a trend toward a higher incidence of solicited systemic reactions in the CYD dengue vaccine (67.5%) compared to Placebo (60.8%), and Control Groups (59.5%). Myalgia in particular has an higher incidence in the CYD dengue vaccine group (40.1%) compared to PBO (34.5%) and control group (34.6%). Malaise has also a slightly higher incidence in the CYD dengue vaccine group (44.2% vs. 39.2% vs. 38.6%, respectively). The 3 other types of solicited systemic reactions were reported with similar frequencies in each groups: headache (51.5%, 48.9%, 47.8%, respectively), asthenia (32.8% vs. 32.4% vs. 29.2%), and fever (19.6%, 18.7%, and 15.7%, respectively).

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

In CYD dengue vaccine group, grade 3 reactions were reported in 1.0% (myalgia) to 3.1% (fever) of subjects, depending on solicited reaction. Grade 3 fever occurred throughout the solicited period D0 to D14 and resolved after 1 to 3 days of occurrence, spontaneously, after a medication or health care provider contact or a combination of both.

As seen before, in baseline seropositive subjects, there was a trend toward a higher incidence of solicited systemic reactions in the CYD dengue vaccine Group (57% vs. 51.8% in PBO vs. 53.3% in control group), and of grade 3 solicited systemic reactions (6.8% vs. 4.5% vs. 4.6%, respectively).

All grade myalgia in particular has an higher incidence in the CYD dengue vaccine group (32.9%) compared to PBO (22.7%) and control group (26.3%). Fever has also a slightly higher incidence in the CYD dengue vaccine group (19.1% vs. 12.7% vs. 11.8%, respectively). The 3 other types of solicited systemic reactions were reported with similar frequencies in each groups: headache (42.5%, 41.8%, 43.4%, respectively), malaise (34.9%, 30.9%, and 32.9%) and asthenia (24.3%, 22.7%, and 25.0%).

Grade 3 myalgia has a slightly higher incidence in the CYD dengue vaccine group (0.7%) compared to PBO (0%) and control group (0%). Grade 3 fever has also a slightly higher incidence in the CYD dengue vaccine group (3.8% vs. 1.8% vs. 2%, respectively). The 3 other types of grade 3 solicited systemic reactions were reported with similar frequencies in each groups: headache (2.7%, 2.7%, 2.6%, respectively), malaise (0.7%, 1.8%, and 1.3%) and asthenia (0.7%, 1.8%, and 1.3%).

In dengue seropositive subjects, solicited systemic reactions, headache, malaise, myalgia, asthenia and fever were observed at a lower frequencies compared to all subjects regardless of baseline dengue serostatus.

After each Injection of the CYD dengue vaccine

The incidence of solicited systemic reactions within 14 days after each CYD dengue vaccine dose is presented in table below.

Table 13: Solicited systemic reactions after each CYD dengue vaccine dose, regardless of baseline dengue serostatus, by maximum intensity during the solicited period – Subjects 6 to 8 years - RS Main Studies Pooled

		Dose 1			Dose 2			Dose 3		
Subjects experiencing at least one:	Maximum intensity	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)
Fever		68/758	9.0	(7.0; 11.2)	65/746	8.7	(6.8; 11.0)	38/735	5.2	(3.7; 7.0)
	Grade 1	35/758	4.6	(3.2; 6.4)	39/746	5.2	(3.7; 7.1)	25/735	3.4	(2.2; 5.0)
	Grade 2	19/758	2.5	(1.5; 3.9)	19/746	2.5	(1.5; 3.9)	9/735	1.2	(0.6; 2.3)
	Grade 3	14/758	1.8	(1.0; 3.1)	7/746	0.9	(0.4; 1.9)	4/735	0.5	(0.1; 1.4)
Headache		272/765	35.6	(32.2; 39.1)	197/750	26.3	(23.1; 29.6)	162/744	21.8	(18.9; 24.9)
	Grade 1	234/765	30.6	(27.3; 34.0)	160/750	21.3	(18.5; 24.4)	135/744	18.1	(15.4; 21.1)
	Grade 2	33/765	4.3	(3.0; 6.0)	28/750	3.7	(2.5; 5.4)	22/744	3.0	(1.9; 4.4)
	Grade 3	5/765	0.7	(0.2; 1.5)	9/750	1.2	(0.6; 2.3)	5/744	0.7	(0.2; 1.6)
Malaise		207/764	27.1	(24.0; 30.4)	170/750	22.7	(19.7; 25.8)	138/744	18.5	(15.8; 21.5)
	Grade 1	168/764	22.0	(19.1; 25.1)	137/750	18.3	(15.6; 21.2)	109/744	14.7	(12.2; 17.4)
	Grade 2	34/764	4.5	(3.1; 6.2)	29/750	3.9	(2.6; 5.5)	26/744	3.5	(2.3; 5.1)
	Grade 3	5/764	0.7	(0.2; 1.5)	4/750	0.5	(0.1; 1.4)	3/744	0.4	(0.1; 1.2)
Myalgia		180/764	23.6	(20.6; 26.7)	165/750	22.0	(19.1; 25.1)	137/744	18.4	(15.7; 21.4)
	Grade 1	153/764	20.0	(17.2; 23.0)	146/750	19.5	(16.7; 22.5)	118/744	15.9	(13.3; 18.7)
	Grade 2	24/764	3.1	(2.0; 4.6)	15/750	2.0	(1.1; 3.3)	18/744	2.4	(1.4; 3.8)
	Grade 3	3/764	0.4	(0.1; 1.1)	4/750	0.5	(0.1; 1.4)	1/744	0.1	(0.0; 0.7)
Asthenia		136/765	17.8	(15.1; 20.7)	122/750	16.3	(13.7; 19.1)	102/744	13.7	(11.3; 16.4)
	Grade 1	105/765	13.7	(11.4; 16.4)	99/750	13.2	(10.9; 15.8)	83/744	11.2	(9.0; 13.6)
	Grade 2	27/765	3.5	(2.3; 5.1)	19/750	2.5	(1.5; 3.9)	18/744	2.4	(1.4; 3.8)
	Grade 3	4/765	0.5	(0.1; 1.3)	4/750	0.5	(0.1; 1.4)	1/744	0.1	(0.0; 0.7)

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

Source: Reproduced from 5.3.5.3 Integrated Safety Analysis Report, Table 3.11.1.21.

Overall, the CHMP considered that in children from 6 to 8 years regardless of baseline dengue serostatus, the incidence of solicited systemic reactions tended to decrease after each injection (48.4%, 40.2%, and 33.2% after the first, second, and third dose, respectively). Similarly, the incidence of each solicited systemic reactions tended to decrease after each injection: headache (35.6%, 26.3%, 21.8% of subjects after the first, second and third dose, respectively), malaise (27.1%, 22.7%, and 18.5%, respectively) and myalgia (23.6%, 22% and 18.4%), and fever (9%, 8.7%, and 5.2%). Grade 3 solicited systemic reaction after any single injection occurred at a frequency equal or below 1.8%. The incidence of Grade 3 fever, the most frequently reported Grade 3 reaction, tended to decrease with subsequent injection.

In baseline seropositive subjects, the incidence of solicited systemic reactions tended to decrease from one injection to the other in the CYD dengue vaccine Group (40.3%, 29.8%, and 26.7% after the first, second, and third dose, respectively). The incidence of fever (7.5%, 7.6%, and 5.3% of subjects after the first, second and third dose, respectively), headache (26.7%, 20.5%, 18.9%, respectively), malaise (22.3%, 15.3%, and 14.4%, respectively), myalgia (18.6%, 17.0%, and 13.3%, respectively), and asthenia (14.0%, 11.1%, and 10.2%, respectively) tended to decrease from one injection to the other.

Unsolicited non-serious adverse events and reactions

Unsolicited non-serious AE

In the CYD dengue vaccine Group, 336 (43.8%) subjects aged 6 to 8 years experienced unsolicited non-serious AEs within 28 days after any injection.

The nature of these AEs in terms of SOCs and PTs could be expected given the age group of the subjects. The most frequently reported unsolicited non-serious AEs were in the SOCs "Infections and infestations" (28.9%), "Respiratory, thoracic and mediastinal disorders" (8.9%), "Gastrointestinal disorders" (7.4%), "General disorders and administration site conditions" (4.3%), and "Injury, poisoning, and procedural complications" (2.5%). The incidence was < 2.5% in the remaining SOCs.

The incidence of unsolicited non-serious AEs tended to decrease with subsequent injections.

Most unsolicited non-serious AEs were Grade 1 and 2, tended to occur either between D0-D3 (13.7%) or ≥ 15 days (13.4%), and had a duration ranging from 1 day to ≤ 8 days. Grade 3 AEs were reported in 2.6% of subjects. The most frequent Grade 3 were in the SOCs "Infections and infestations" (1.6%), "Gastrointestinal disorders" (0.7%), and "Respiratory, thoracic and mediastinal disorders" (0.3%). The incidence was equal or below 0.1% in the remaining SOCs.

In the Placebo Group, the incidence of unsolicited non-serious AEs within 28 days after any injection (44.2%) was similar to that reported in the CYD dengue vaccine Group (43.8%). Similar to what was observed in the CYD dengue vaccine Group, the most frequently reported AEs in the Placebo Group were in the SOCs "Infections and infestations" (29.1%), "Respiratory, thoracic and mediastinal disorders" (9.4%), "Gastrointestinal disorders" (6.5%), and "General disorders and administration site conditions" (4.7%). The incidence was < 3.0% in the remaining SOCs. The incidence of Grade 3 unsolicited non-serious AEs in the Placebo Group was 4.3%.

In the Control Group, the incidence of unsolicited non-serious AEs within 28 days after any injection (45.7%) was similar to that reported in the CYD dengue vaccine Group (43.1%). Similar to what was observed in both the CYD dengue vaccine and Placebo Groups, the most frequently reported AEs in the Control Group were in the SOCs "Infections and infestations" (31.4%), "Respiratory, thoracic and mediastinal disorders" (8.9%), "Gastrointestinal disorders" (7.6%), and "General disorders and administration site conditions" (4.3%). The incidence was < 3.0% in the remaining SOCs. The incidence of Grade 3 unsolicited non-serious AEs in the Control Group was 3.5%.

In baseline seropositive subjects, the incidence of unsolicited non-serious AEs after any of 3 doses in the CYD dengue vaccine Placebo, and Control Groups was 37.4%, 40.9%, and 45.4%, respectively. The incidence of unsolicited non-serious AEs in the CYD dengue vaccine Group tended to decrease after each subsequent injection with 21.8% of subjects after the first injection, 15.6% after the second injection, and 13.0% after the third injection.

Unsolicited non-serious AR

Unsolicited non-serious ARs within 28 days after any CYD dengue vaccine, placebo or control injection are presented for children aged 6 to 8 years in the Main Studies in table below. ARs occurring in at least 2 (0.3%) subjects in the CYD dengue vaccine Group are displayed in the table for the CYD dengue vaccine, Placebo and Control Groups. In addition, each SOC with an incidence of ≥ 0.3%, even if ARs in this SOC are reported in less than 0.3% of subjects, is presented in the table.

Table 14: Unsolicited non-serious ARs reported in at least 0.1% of subjects within 28 days after any of 3 doses of CYD dengue vaccine or Placebo or Control, regardless of baseline dengue serostatus, by SOC and PT - Subjects 6 to 8 years - RS Main Studies Pooled

	CYD dengue vaccine				Placebo				Control			
Subjects experiencing at least one:	n/N	%	(95% CI)	n ARs	n/N	%	(95% CI)	n ARs	n/N	%	(95% CI)	n ARs
Unsolicited non-serious AR	24/768	3.1	(2.0; 4.6)	33	5/278	1.8	(0.6; 4.1)	7	6/370	1.6	(0.6; 3.5)	9
General disorders and administration site conditions	13/768	1.7	(0.9; 2.9)	14	3/278	1.1	(0.2; 3.1)	4	3/370	0.8	(0.2; 2.4)	4
Injection site hemorrhage	3/768	0.4	(0.1; 1.1)	3	0/278	0.0	(0.0; 1.3)	0	0/370	0.0	(0.0; 1.0)	0
Injection site induration	3/768	0.4	(0.1; 1.1)	4	1/278	0.4	(0.0; 2.0)	1	1/370	0.3	(0.0; 1.5)	1
Injection site bruising	2/768	0.3	(0.0; 0.9)	2	0/278	0.0	(0.0; 1.3)	0	0/370	0.0	(0.0; 1.0)	0
Gastrointestinal disorders	8/768	1.0	(0.5; 2.0)	8	1/278	0.4	(0.0; 2.0)	2	2/370	0.5	(0.1; 1.9)	3
Vomiting	7/768	0.9	(0.4; 1.9)	7	0/278	0.0	(0.0; 1.3)	0	1/370	0.3	(0.0; 1.5)	1
Metabolism and nutrition disorders	3/768	0.4	(0.1; 1.1)	4	0/278	0.0	(0.0; 1.3)	0	0/370	0.0	(0.0; 1.0)	0
Decreased appetite	3/768	0.4	(0.1; 1.1)	4	0/278	0.0	(0.0; 1.3)	0	0/370	0.0	(0.0; 1.0)	0
Infections and infestations	2/768	0.3	(0.0; 0.9)	2	0/278	0.0	(0.0; 1.3)	0	0/370	0.0	(0.0; 1.0)	0
Skin and subcutaneous tissue disorders	2/768	0.3	(0.0; 0.9)	2	0/278	0.0	(0.0; 1.3)	0	0/370	0.0	(0.0; 1.0)	0

n: number of subjects experiencing the endpoint
n ARs: number of ARs
N: total number of subjects per dose
CYD dengue vaccine 5 ± 1 log10 CCID50 of serotypes 1, 2, 3 and 4
Main studies applied a D0/M6/M12 vaccine schedule
Contributing studies: CYD14 CYD22 CYD23 CYD24 CYD28 CYD32

Source: modified from 5.3.5.3 Integrated Safety Analysis Report, Table 3.11.1.29.

Maximum intensity, maximum duration, and shortest time to onset are presented in table below.

Table 15: Unsolicited non-serious ARs within 28 days after any of 3 doses of CYD dengue vaccine or Placebo Control, regardless of baseline dengue serostatus, by maximum intensity, maximum duration and earliest time to onset - Subjects 6 to 8 years - RS Main Studies Pooled

	CYD dengue vaccine			Placebo			Control		
Subjects experiencing at least one:	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)
Unsolicited non-serious AR	24/768	3.1	(2.0; 4.6)	5/278	1.8	(0.6; 4.1)	6/370	1.6	(0.6; 3.5)
Max intensity									
Missing	4/768	0.5	(0.1; 1.3)	0/278	0.0	(0.0; 1.3)	0/370	0.0	(0.0; 1.0)
Grade 1	14/768	1.8	(1.0; 3.0)	4/278	1.4	(0.4; 3.6)	5/370	1.4	(0.4; 3.1)
Grade 2	5/768	0.7	(0.2; 1.5)	1/278	0.4	(0.0; 2.0)	1/370	0.3	(0.0; 1.5)
Grade 3	1/768	0.1	(0.0; 0.7)	0/278	0.0	(0.0; 1.3)	0/370	0.0	(0.0; 1.0)
Max duration									
Missing	1/768	0.1	(0.0; 0.7)	0/278	0.0	(0.0; 1.3)	0/370	0.0	(0.0; 1.0)
1-3 days	14/768	1.8	(1.0; 3.0)	4/278	1.4	(0.4; 3.6)	5/370	1.4	(0.4; 3.1)
4-7 days	6/768	0.8	(0.3; 1.7)	1/278	0.4	(0.0; 2.0)	1/370	0.3	(0.0; 1.5)
8 days or more	3/768	0.4	(0.1; 1.1)	0/278	0.0	(0.0; 1.3)	0/370	0.0	(0.0; 1.0)
Earliest time to onset									
Missing	1/768	0.1	(0.0; 0.7)	0/278	0.0	(0.0; 1.3)	0/370	0.0	(0.0; 1.0)
D0-D3	18/768	2.3	(1.4; 3.7)	4/278	1.4	(0.4; 3.6)	4/370	1.1	(0.3; 2.7)
D4-D7	2/768	0.3	(0.0; 0.9)	0/278	0.0	(0.0; 1.3)	0/370	0.0	(0.0; 1.0)
D8-D14	2/768	0.3	(0.0; 0.9)	0/278	0.0	(0.0; 1.3)	0/370	0.0	(0.0; 1.0)
>= D15	1/768	0.1	(0.0; 0.7)	1/278	0.4	(0.0; 2.0)	2/370	0.5	(0.1; 1.9)

Table summarizes worst case for a subject which is maximum intensity, maximum duration and earliest time to onset observed from each dose

n: number of subjects experiencing the endpoint

N: total number of subjects per dose

CYD dengue vaccine 5 ± 1 log10 CCID50 of serotypes 1, 2, 3 and 4

Main studies applied a D0/M6/M12 vaccine schedule

Contributing studies: CYD14 CYD22 CYD23 CYD24 CYD28 CYD32

Source: modified from 5.3.5.3 Integrated Safety Analysis Report, Table 3.11.1.32.

In the CYD dengue vaccine Group, a total of 3.1% of subjects experienced unsolicited nonserious ARs within 28 days after any CYD dengue vaccine injection.

The most frequently reported unsolicited non-serious ARs after any CYD dengue vaccine injection were vomiting (0.9%), injection site hemorrhage, injection site induration, decreased appetite (0.4% each), and injection site bruising (0.3%). The other PTs accounted for less than 0.3% each.

The proportion of subjects with unsolicited non-serious ARs was similar after each subsequent injection with 2.0%, 1.1%, and 0.5% after the first, second, and third injection, respectively.

Most unsolicited non-serious ARs were Grade 1 or 2, tended to occur either between D0-D3, and had a duration ranging from 1 to 3 days. One of these ARs led to study discontinuation (a Grade 2 urticaria; see section 2.3.1.1.).

A single (0.1%) subject experienced a Grade 3 vomiting: a 7-year-old subject (Subject 004-10038 in CYD32) experienced Grade 3 vomiting on D1 after the third injection. The event resolved spontaneously after 2 days.

The CHMP considered that, of note, vomiting is an identified ADR of dengvaxia for children.

In the Placebo Group, unsolicited non-serious ARs tended to be reported at a frequency (5 subjects, 1.8 %) somewhat lower than in the CYD dengue vaccine Group (24 subjects, 3.1%). ARs were isolated in terms of nature as no PTs were reported in more than 1 subject. No Grade 3 ARs were reported in the Placebo Group.

In the Control Group, unsolicited non-serious ARs were also reported at a lower frequency (6 subjects, 1.6 %) than in the CYD dengue vaccine Group (24 subjects, 3.1%). ARs were isolated in terms of nature as no PTs were reported in more than 1 subject. No Grade 3 ARs were reported in the Control Group.

There were 2 occurrences of Nervous system disorder AR reported in subjects aged 6 to 8 years; dizziness was experienced by 1 subject in the CYD dengue vaccine Group and headache was reported in 1 subject from the Control Group.

In addition to the intensity grading, all ARs were reviewed for clinical relevance and no concern was raised in the CYD dengue vaccine Group.

In baseline seropositive subjects, the incidence of unsolicited non-serious ARs after any of 3 doses in the CYD dengue vaccine, Placebo, and Control Groups was 1.7%, 2.7%, and 2.0%, respectively. The incidence of unsolicited non-serious ARs tended to remain similar after each subsequent injection; with 1.0% of subjects after the first and second injections and 0% after the third injection.

2.3.1.2. Serious adverse event/deaths/other significant events

Deaths

No death was reported in the CYD dengue vaccine Group within 6 months after any injection in the Main Studies.

In the Placebo / Control Group, 5 (0.3%) deaths occurred in the Main Studies within 6 months after any injection (acute lymphoblastic leukemia, drowning, head injury, T-cell lymphoma, and road traffic accident). None were assessed as related to the injection by the Investigator or the Sponsor.

In All Studies, no additional deaths were reported in the CYD dengue vaccine Group within 6 months after any injection.

Deaths that occurred more than 6 months after the last injection were presented. None were assessed as related to the study vaccination.

Serious adverse events

SAEs, including related SAEs, during the LTFU, i.e. more than 6 months after the last injection were presented, and so were SAEs leading to study discontinuation.

SAEs Within 28 Days After Any of 3 Doses

SAEs that occurred within 28 days after any injection in children aged 6 to 8 years, regardless of baseline serostatus, are displayed in Table below. SAEs reported in at least 0.1% of subjects in the CYD dengue vaccine Group are displayed for the CYD dengue vaccine, Placebo, and Control Groups. In addition, each SOC with an incidence of ≥ 0.1%, even if SAEs in this SOC are reported in less than 0.1% of subjects, is presented in the following table.

Table 16: All and related SAEs <= 28 days after any of 3 doses of CYD dengue vaccine or Placebo or Control, regardless of baseline dengue serostatus, by main SOC and PT - Subjects 6 to 8 years - SafAS Main Studies Pooled

	CYD dengue vaccine								Placebo								Control							
	All SAEs				Related SAEs				All SAEs				Related SAEs				All SAEs				Related SAEs			
Subjects experiencing at least one:	n/N	%	(95% CI)	n SAEs	n/N	%	(95% CI)	n SAEs	n/N	%	(95% CI)	n SAEs	n/N	%	(95% CI)	n SAEs	n/N	%	(95% CI)	n SAEs	n/N	%	(95% CI)	n SAEs
SAE	41/3233	1.3	(0.91; 1.72)	44	1/3233	<0.1	(0.00; 0.17)	1	28/1505	1.9	(1.24; 2.68)	30	2/1505	0.1	(0.02; 0.48)	2	29/1597	1.8	(1.22; 2.60)	31	2/1597	0.1	(0.02; 0.45)	2
Infections and infestations	21/3233	0.6	(0.40; 0.99)	22	0/3233	0.0	(0.00; 0.11)	0	19/1505	1.3	(0.76; 1.96)	20	0/1505	0.0	(0.00; 0.24)	0	19/1597	1.2	(0.72; 1.85)	20	0/1597	0.0	(0.00; 0.23)	0
Gastroenteritis	5/3233	0.2	(0.05; 0.36)	5	0/3233	0.0	(0.00; 0.11)	0	1/1505	<0.1	(0.00; 0.37)	1	0/1505	0.0	(0.00; 0.24)	0	1/1597	<0.1	(0.00; 0.35)	1	0/1597	0.0	(0.00; 0.23)	0
Injury, poisoning and procedural complications	8/3233	0.2	(0.11; 0.49)	8	0/3233	0.0	(0.00; 0.11)	0	1/1505	<0.1	(0.00; 0.37)	1	0/1505	0.0	(0.00; 0.24)	0	2/1597	0.1	(0.02; 0.45)	2	0/1597	0.0	(0.00; 0.23)	0
Gastrointestinal disorders	4/3233	0.1	(0.03; 0.32)	5	0/3233	0.0	(0.00; 0.11)	0	2/1505	0.1	(0.02; 0.48)	2	0/1505	0.0	(0.00; 0.24)	0	2/1597	0.1	(0.02; 0.45)	2	0/1597	0.0	(0.00; 0.23)	0

n: number of subjects experiencing the endpoint
n SAEs: number of SAEs
N: total number of subjects per dose
CYD dengue vaccine 5 ± 1 log10 CCID50 of serotypes 1, 2, 3 and 4
Main studies applied a D0/M6/M12 vaccine schedule
Contributing studies: CYD14 CYD22 CYD23 CYD24 CYD28 CYD32

Source: modified from 5.3.5.3 Integrated Safety Analysis Report, Table 3.11.1.34.

A total of 41 out of 3233 (1.3%) subjects aged 6 to 8 years in the CYD dengue vaccine Group experienced 44 SAEs within 28 days after any injection. The proportion of subjects who experienced at least 1 SAE was similar (or slightly less) to that observed in the Placebo and Control Groups with 1.9% and 1.8% of subjects experiencing SAEs, respectively.

For the 41 subjects who experienced SAEs in the CYD dengue vaccine Group, all SAEs were considered as serious because of either "required or prolonged inpatient hospitalization" (39 subjects) or "other important medical event" (3 subjects). No deaths were reported and all subjects with an SAE occurring within 28 days after any injection recovered.

In all 3 groups, most of the SAEs were in the SOC "Infections and infestations" with 0.6%, 1.3%, and 1.2% of subjects in the CYD dengue vaccine, Placebo, and Control Groups, respectively. In the CYD dengue vaccine Group, besides the SOCs "Injury, poisoning, and procedural complications" (0.2%) and "Gastrointestinal disorders" (0.1%), SAEs in other SOCs were all reported in less than 0.1% of subjects.

In the CYD dengue vaccine group, in the SOC "Injury, poisoning, and procedural complications", the 8 SAEs were the following: epiphyseal injury, forearm fracture, foreign body, hand fracture, joint injury, road traffic accident, snake bite and traumatic haemorrhage (skin laceration in placebo group; skin laceration and vulvovaginal injury in control group). In the SOC "Gastrointestinal disorders", the 4 SAEs were the following: 4 gastritis and 1 salivary gland mucocele (2 gastritis each in placebo and control groups).

When considering each injection, there was a trend toward a decrease incidence of SAEs within 28 days with subsequent injections. The incidence of SAEs was 0.7%, 0.4%, and 0.3% after the first, second and third injection, respectively.

In the CYD dengue vaccine Group, there was 1 (< 0.1%) neurological disorder SAE and it was the only SAE assessed as related to the study vaccine by the Investigator: an 8-year-old subject (Subject 220-00332 in CYD14) experienced an acute disseminated encephalomyelitis on D7 after the first injection. The event lasted 14 days and led to discontinuation from the study. The subject fully recovered.

In the Placebo and Control Groups, there were 3 neurological disorder SAEs reported in each group (0.2% for each group): epilepsy, facial paralysis, and seizure were each reported once; facial paralysis in both groups was assessed as related to the injection by the Investigator or the Sponsor.

In total, in each of the Placebo and Control Groups, 2 (0.1%) subjects experienced SAEs that were assessed as related to the study vaccine by the Investigator or by the Sponsor: facial paralysis and angioedema.

The CHMP noted that Subject 220-00332 presented a related SAE of acute disseminated encephalomyelitis (ADEM) in the CYD dengue vaccine group 7 days after the first study vaccination. Vaccinal and wild-type dengue virus test was negative in serum, blood, urine and cerebrospinal fluid. Therefore, a neurotropic disease with replication of the vaccinal virus in the CNS was excluded.

Five subjects reported gastroenteritis SAE in the CYD dengue vaccine group within 9 to 27 days after the first or the second injection (compared to 1 gastroenteritis SAE each in placebo and control groups). The most common etiology of gastroenteritis in children is infectious (viral or bacterial origin). In these 5 cases, the symptomatology, the course of the disease, investigations (e.g., laboratory) and rapid resolution after initiation of treatment, mainly IV fluids and antibiotics, confirm the diagnosis of gastroenteritis of infectious origin (bacteria, except two with possible viral etiology). In addition, the absence of pattern in the latency period between onset of events and last CYD dengue vaccine does not raise suspicion on the role of the study vaccine. All gastroenteritis events were assessed to be not related to the study vaccine by the investigators, in agreement with the sponsor.

In the CYD dengue vaccine Group in all studies, 41 out of 3253 (1.3%) subjects reported at least 1 SAE within 28 days after any injection. Compared to the Main Studies, there were no additional SAEs to report in the All Studies set.

In baseline seropositive subjects (main studies), the incidence of SAE within 28 days after any 3 doses in the CYD dengue vaccine, Placebo, and Control Groups was 1.4%, 1.8%, and 2.0%, respectively (without any related SAE). In baseline seropositive subjects, the incidence of SAE within 28 days tended to remain similar after each subsequent injection; with 1.0% of subjects after the first, 0% after the second injection, and 0.4% after the third injection.

SAEs more than 28 Days and up to 6 months After Any of 3 Doses

SAEs that occurred after 28 days and up to 6 months after any injection in children aged 6 to 8 years, regardless of baseline serostatus, are displayed in Table below. SAEs reported in at least 0.1% of subjects in the CYD dengue vaccine Group are displayed for the CYD dengue vaccine, Placebo, and Control Groups. In addition, each SOC with an incidence of ≥ 0.1%, even if SAEs in this SOC are reported in less than 0.1% of subjects, is presented in the table below.

Table 17: All and related SAEs > 28 days to 6-months after any of 3 doses of CYD dengue vaccine or Placebo or Control, regardless of baseline dengue serostatus, by main SOC and PT - Subjects 6 to 8 years - SafAS Main Studies Pooled

	CYD dengue vaccine								Placebo								Control							
	All SAEs				Related SAEs				All SAEs				Related SAEs				All SAEs				Related SAEs			
Subjects experiencing at least one:	n/N	%	(95% CI)	n SAEs	n/N	%	(95% CI)	n SAEs	n/N	%	(95% CI)	n SAEs	n/N	%	(95% CI)	n SAEs	n/N	%	(95% CI)	n SAEs	n/N	%	(95% CI)	n SAEs
SAE	181/3233	5.6	(4.83; 6.45)	197	0/3233	0.0	(0.00; 0.11)	0	105/1505	7.0	(5.74; 8.38)	125	0/1505	0.0	(0.00; 0.24)	0	110/1597	6.9	(5.69; 8.24)	130	0/1597	0.0	(0.00; 0.23)	0
Infections and infestations	117/3233	3.6	(3.00; 4.32)	126	0/3233	0.0	(0.00; 0.11)	0	67/1505	4.5	(3.47; 5.62)	77	0/1505	0.0	(0.00; 0.24)	0	71/1597	4.4	(3.49; 5.58)	81	0/1597	0.0	(0.00; 0.23)	0
Dengue fever	17/3233	0.5	(0.31; 0.84)	17	0/3233	0.0	(0.00; 0.11)	0	12/1505	0.8	(0.41; 1.39)	12	0/1505	0.0	(0.00; 0.24)	0	12/1597	0.8	(0.39; 1.31)	12	0/1597	0.0	(0.00; 0.23)	0
Pharyngitis	16/3233	0.5	(0.28; 0.80)	18	0/3233	0.0	(0.00; 0.11)	0	5/1505	0.3	(0.11; 0.77)	5	0/1505	0.0	(0.00; 0.24)	0	6/1597	0.4	(0.14; 0.82)	6	0/1597	0.0	(0.00; 0.23)	0
Bronchitis	14/3233	0.4	(0.24; 0.73)	14	0/3233	0.0	(0.00; 0.11)	0	6/1505	0.4	(0.15; 0.87)	6	0/1505	0.0	(0.00; 0.24)	0	6/1597	0.4	(0.14; 0.82)	6	0/1597	0.0	(0.00; 0.23)	0
Gastroenteritis	14/3233	0.4	(0.24; 0.73)	14	0/3233	0.0	(0.00; 0.11)	0	7/1505	0.5	(0.19; 0.96)	7	0/1505	0.0	(0.00; 0.24)	0	7/1597	0.4	(0.18; 0.90)	7	0/1597	0.0	(0.00; 0.23)	0
Cellulitis	6/3233	0.2	(0.07; 0.40)	6	0/3233	0.0	(0.00; 0.11)	0	0/1505	0.0	(0.00; 0.24)	0	0/1505	0.0	(0.00; 0.24)	0	0/1597	0.0	(0.00; 0.23)	0	0/1597	0.0	(0.00; 0.23)	0
Pharyngotonsillitis	5/3233	0.2	(0.05; 0.36)	6	0/3233	0.0	(0.00; 0.11)	0	4/1505	0.3	(0.07; 0.68)	4	0/1505	0.0	(0.00; 0.24)	0	4/1597	0.3	(0.07; 0.64)	4	0/1597	0.0	(0.00; 0.23)	0
Tonsillitis	5/3233	0.2	(0.05; 0.36)	5	0/3233	0.0	(0.00; 0.11)	0	2/1505	0.1	(0.02; 0.48)	3	0/1505	0.0	(0.00; 0.24)	0	2/1597	0.1	(0.02; 0.45)	3	0/1597	0.0	(0.00; 0.23)	0
Viral infection	5/3233	0.2	(0.05; 0.36)	5	0/3233	0.0	(0.00; 0.11)	0	5/1505	0.3	(0.11; 0.77)	5	0/1505	0.0	(0.00; 0.24)	0	6/1597	0.4	(0.14; 0.82)	6	0/1597	0.0	(0.00; 0.23)	0
Injury, poisoning and procedural complications	22/3233	0.7	(0.43; 1.03)	22	0/3233	0.0	(0.00; 0.11)	0	12/1505	0.8	(0.41; 1.39)	12	0/1505	0.0	(0.00; 0.24)	0	13/1597	0.8	(0.43; 1.39)	13	0/1597	0.0	(0.00; 0.23)	0
Gastrointestinal disorders	32/3233	1.0	(0.68; 1.39)	33	0/3233	0.0	(0.00; 0.11)	0	12/1505	0.8	(0.41; 1.39)	12	0/1505	0.0	(0.00; 0.24)	0	12/1597	0.8	(0.39; 1.31)	12	0/1597	0.0	(0.00; 0.23)	0
Gastritis	18/3233	0.6	(0.33; 0.88)	19	0/3233	0.0	(0.00; 0.11)	0	11/1505	0.7	(0.37; 1.30)	11	0/1505	0.0	(0.00; 0.24)	0	11/1597	0.7	(0.34; 1.23)	11	0/1597	0.0	(0.00; 0.23)	0
Food poisoning	4/3233	0.1	(0.03; 0.32)	4	0/3233	0.0	(0.00; 0.11)	0	1/1505	<0.1	(0.00; 0.37)	1	0/1505	0.0	(0.00; 0.24)	0	1/1597	<0.1	(0.00; 0.35)	1	0/1597	0.0	(0.00; 0.23)	0
Nervous system disorders	4/3233	0.1	(0.03; 0.32)	4	0/3233	0.0	(0.00; 0.11)	0	4/1505	0.3	(0.07; 0.68)	4	0/1505	0.0	(0.00; 0.24)	0	4/1597	0.3	(0.07; 0.64)	4	0/1597	0.0	(0.00; 0.23)	0

n: number of subjects experiencing the endpoint
n SAEs: number of SAEs
N: total number of subjects per dose
CYD dengue vaccine 5 ± 1 log10 CCID50 of serotypes 1, 2, 3 and 4
Main studies applied a D0/M6/M12 vaccine schedule
Contributing studies: CYD14 CYD22 CYD23 CYD24 CYD28 CYD32

Source: modified from 5.3.5.3 Integrated Safety Analysis Report, Table 3.11.1.37.

A total of 181 out of 3233 (5.6%) subjects aged 6 to 8 years in the CYD dengue vaccine Group experienced 197 SAEs after 28 days and up to 6 months after any injection, which was less that in the Placebo Group (105 subjects reported a total of 125 SAEs - 7%) and in the control group (a total of 110 subjects experienced 130 SAEs – 6.9%).

For the 181 subjects who experienced SAEs in the CYD dengue vaccine Group, all SAEs were considered as serious because of either "required or prolonged inpatient hospitalization" (179 subjects) and/or "other important medical event" (5 subjects).

Within 6 months after any injection, there were no deaths reported in the CYD dengue vaccine Group. Most subjects with SAEs after 28 days and up to 6 months after any injection recovered. One subject recovered with sequelae from an SAE (road traffic accident) while another subject's SAE (epilepsy) was ongoing.

In the 3 groups, most of the SAEs were in the SOC Infections and infestations (3.6% of subjects in the CYD dengue vaccine Group; 4.5% and 4.4% in the Placebo and Control Groups, respectively), "Gastrointestinal disorders" (1.0% in the CYD dengue vaccine Group; 0.8% in the Placebo and Control Groups), "Injury, poisoning and procedural complications (0.7% in the CYD dengue vaccine Group; 0.8% in the Placebo and Control Groups), and "Nervous system disorders" (0.1% in the CYD dengue vaccine Group; 0.3% in the Placebo and Control Groups). In the CYD dengue vaccine Group, SAEs in the other SOCs were all reported in ≤ 0.1% of subjects.

The incidence of SAEs after each injection tended to be similar with 1.9%, 2.3%, and 1.7% after the first, second and third injection, respectively.

In the CYD dengue vaccine Group, 4 (0.1%) neurological disorder SAEs were reported. Each PT were reported once (epilepsy, febrile convulsion, ischemic stroke, and seizure) and none were assessed as related to the study vaccine. In the Placebo and Control Groups, there were also 4 neurological disorder SAEs reported in each group (0.3% for each group). Epilepsy, febrile convulsion, ischemic stroke, and seizure were each reported once. None was assessed as related to the injection by the Investigator or the Sponsor.

No SAEs were assessed as related to the study vaccine by the Investigator between 28 days and 6 months after any injection in any of the groups.

In the CYD dengue vaccine Group in all studies, 181 out of 3253 (5.6%) subjects reported at least 1 SAE after 28 days and up to 6 months after any injection. Compared to the Main Studies, there were no additional SAEs to report in the All Studies set.

In baseline seropositive subjects (main studies), the incidence of SAEs after 28 days and up to 6 months after any injection in the CYD dengue vaccine, Placebo, and Control Groups was 5.8%, 5.5%, and 5.3%, respectively. The incidence of SAE after 28 days and up to 6 months after injection tended to remain similar after each subsequent injection; with 3.1% of subjects after the first, and 1.4% after the second and third injections.

The CHMP noted that four subjects presented a neurological disorder SAE (epilepsy, febrile convulsion, ischemic stroke, and seizure) in the CYD dengue vaccine group after 30 days and up to 6 months after any injection (0.1%). There were also 4 neurological disorder SAEs reported respectively in Placebo and Control Group (0.3% for each group). All neurological disorder SAEs were assessed as not related to the study vaccine per investigator and sponsor.

These 4 cases of neurological disorders (epilepsy, febrile convulsion, ischemic stroke and seizure) occurred in children from 7 to 9 years old. The febrile convulsion was caused by a spike at 40.2°C in body temperature, from infectious origin. The epilepsy event was diagnosed and occurred with a long latency (91 days) after receiving the second dose of CYD dengue vaccine. For the seizure event, although the cause of this seizure episode was not identified, the child experienced this episode for the first time with a long latency (more than five and half months) after 3rd vaccine injection. No other episode was reported for this child during the study (safety follow-up for 36 months after the 3rd injection).

The last neurological disorder was an ischemic stroke with unclear etiology. However, clinical symptoms, symptoms chronology, investigations results and long latency (> 5 months) after 2nd vaccine injection are not suggestive of a link with the vaccine.

Six subjects reported cellulitis SAE in the CYD dengue vaccine group (0.2%) after 28 days and up to 6 months after any injection (compared to no subject with cellulitis SAE in placebo and control groups).

In all these cases, cellulitis can be explained by alternative etiology (infected impetigo, insect bite, dental root abscess, green pit viper bite, after accident/fall). The nature, the chronology of the disease and the long latency (> 2 months) after last CYD dengue vaccine injection is not suggestive of any relationship to the study vaccine. Also, the recovery of the events after corrective treatment (including antibiotics), is suggestive of infectious in nature. All events were assessed to be not related to the study vaccine by the investigators, in agreement with the sponsor.

2.3.1.1. AE leading to discontinuation (withdrawn from further injections)

In the main Studies (SafAS: 3233 subjects and RS: 768 subjects), as per the information reported in the termination form, the proportion of subjects who discontinued due to a non-serious AE or a SAE

tended to be lower in the CYD dengue vaccine Group (0.2%; 8 subjects) compared to that in the Placebo / Control Group (0.8% ; 12 subjects each).

In the CYD dengue vaccine Group, 4 subjects discontinued due to non-serious AEs. Among these, one subject discontinued due to a Grade 2 urticaria after the second injection. For the remaining 3 subjects that discontinued due to non-serious AEs, AEs were not detailed in an AE form but were mentioned in the Investigator's comment of the termination form of the CRF as the reason for study discontinuation. These AEs were identified as: illness after vaccination, generalized itching rash, and urticaria.

In the Placebo Group, 2 subjects discontinued due to unsolicited non-serious AEs. One subject discontinued due to a Grade 1 hypersensitivity after the second injection; the AE was assessed as related to placebo injection by Investigator. For the other subject, the non-serious AE of "frequent fever" was mentioned in the Investigator's comment of the CRF termination form as the reason for study discontinuation.

In the CYD dengue vaccine Group, SAEs leading to discontinuation after any injection were reported in 4 subjects. No trend was observed regarding the distribution of SAEs within the different SOCs. At the PT level, most SAEs were isolated in terms of nature and were reported as isolated events: rheumatic heart disease, acute disseminated encephalomyelitis, ischemic stroke, and nephrotic syndrome. Among these SAEs, acute disseminated encephalomyelitis was assessed as related to the study vaccine by the Investigator or the Sponsor.

In the Placebo Group, SAEs leading to study discontinuation after any injection were reported in 10 subjects. No trend was observed regarding the distribution of SAEs within the different SOCs. At the PT level, most SAEs were isolated in terms of nature and were reported as isolated events: angioedema with generalized urticaria, ischemic stroke, acute lymphocytic leukemia, epilepsy, encephalitis, drowning, T-cell lymphoma, road traffic accident, head injury, and facial paralysis. Among these SAEs, angioedema with generalized urticaria and facial paralysis were assessed as related to placebo injection by the Investigator.

In all Studies (SafAS: 3253 subjects and RS: 788 subjects), in the CYD dengue vaccine Group, compared to the Main Studies, 1 additional subject was discontinued due to a non-serious AE (eosinophilia assessed as not related to study vaccine). There were no additional SAEs leading to study discontinuation.

2.3.2. Comparison to safety overview in subjects aged 9 to 17 years

Safety Overview After Any Injection

A safety overview for the Main Studies in which the CYD dengue vaccine was administered as a 3-dose schedule (injection at 6-month intervals) is presented for children/adolescents aged 9 to 17 years after any CYD dengue vaccine, placebo, or control injection in table below.

Table 18: Safety overview after any of 3 doses of CYD dengue vaccine or Placebo or Control, regardless of baseline dengue serostatus - Subjects 9 to 17 years - SafAS Main Studies Pooled

	CYD dengue vaccine			Placebo			Control		
Subjects experiencing at least one:	n/M	%	(95% CI)	n/M	%	(95% CI)	n/M	%	(95% CI)
REACTOGENICITY SUBSET									
Immediate unsolicited AE	6/3666	0.2	(0.1; 0.4)	1/1152	<0.1	(0.0; 0.5)	3/1481	0.2	(0.0; 0.6)
Immediate unsolicited AR	3/3666	<0.1	(0.0; 0.2)	1/1152	<0.1	(0.0; 0.5)	1/1481	<0.1	(0.0; 0.4)
Grade 3 immediate unsolicited AR	1/3666	<0.1	(0.0; 0.2)	0/1152	0.0	(0.0; 0.3)	0/1481	0.0	(0.0; 0.2)
Solicited reaction	2687/3647	73.7	(72.2; 75.1)	824/1146	71.9	(69.2; 74.5)	1080/1474	73.3	(70.9; 75.5)
Grade 3 solicited reaction	403/3647	11.1	(10.1; 12.1)	105/1146	9.2	(7.6; 11.0)	141/1474	9.6	(8.1; 11.2)
Solicited injection site reaction	1883/3647	51.6	(50.0; 53.3)	497/1145	43.4	(40.5; 46.3)	717/1473	48.7	(46.1; 51.3)
Grade 3 solicited injection site reaction	56/3647	1.5	(1.2; 2.0)	11/1145	1.0	(0.5; 1.7)	21/1473	1.4	(0.9; 2.2)
Solicited systemic reaction	2387/3647	65.5	(63.9; 67.0)	754/1146	65.8	(63.0; 68.5)	977/1474	66.3	(63.8; 68.7)
Grade 3 solicited systemic reaction	380/3647	10.4	(9.4; 11.5)	104/1146	9.1	(7.5; 10.9)	133/1474	9.0	(7.6; 10.6)
Unsolicited non-serious AE	1496/3666	40.8	(39.2; 42.4)	480/1152	41.7	(38.8; 44.6)	651/1481	44.0	(41.4; 46.5)
Unsolicited non-serious AR	80/3666	2.2	(1.7; 2.7)	8/1152	0.7	(0.3; 1.4)	19/1481	1.3	(0.8; 2.0)
Grade 3 unsolicited non-serious AR	9/3666	0.2	(0.1; 0.5)	0/1152	0.0	(0.0; 0.3)	1/1481	<0.1	(0.0; 0.4)
Unsolicited non-serious injection site AR	43/3666	1.2	(0.9; 1.6)	5/1152	0.4	(0.1; 1.0)	9/1481	0.6	(0.3; 1.2)
Grade 3 unsolicited non-serious injection site AR	0/3666	0.0	(0.0; 0.1)	0/1152	0.0	(0.0; 0.3)	0/1481	0.0	(0.0; 0.2)
Unsolicited non-serious systemic AE	1484/3666	40.5	(38.9; 42.1)	478/1152	41.5	(38.6; 44.4)	649/1481	43.8	(41.3; 46.4)
Unsolicited non-serious systemic AR	39/3666	1.1	(0.8; 1.5)	3/1152	0.3	(0.1; 0.8)	10/1481	0.7	(0.3; 1.2)
Grade 3 unsolicited non-serious systemic AR	9/3666	0.2	(0.1; 0.5)	0/1152	0.0	(0.0; 0.3)	1/1481	<0.1	(0.0; 0.4)
Anaphylactic reaction (SMQ)	0/3666	0.0	(0.0; 0.1)	0/1152	0.0	(0.0; 0.3)	0/1481	0.0	(0.0; 0.2)
Non-serious allergic reaction (targeted list)	18/3666	0.5	(0.3; 0.8)	5/1152	0.4	(0.1; 1.0)	10/1481	0.7	(0.3; 1.2)
Non-serious Grade 3 allergic reaction (targeted list)	1/3666	<0.1	(0.0; 0.2)	0/1152	0.0	(0.0; 0.3)	0/1481	0.0	(0.0; 0.2)
Post-vaccination dengue-like syndrome	2/3666	<0.1	(0.0; 0.2)	0/1152	0.0	(0.0; 0.3)	0/1481	0.0	(0.0; 0.2)
SAFETY ANALYSIS SET									
Discontinuation due to AE*	78/19715	0.4	(0.31; 0.49)	43/9163	0.5	(0.34; 0.63)	44/9492	0.5	(0.34; 0.62)
Serious allergic reaction (targeted list)	4/19715	<0.1	(0.01; 0.05)	1/9163	<0.1	(0.00; 0.06)	1/9492	<0.1	(0.00; 0.06)
SAE <=28 days post dose	127/19715	0.6	(0.54; 0.77)	70/9163	0.8	(0.60; 0.96)	76/9492	0.8	(0.63; 1.00)
SAE >28 days to 6 months post dose	547/19715	2.8	(2.55; 3.01)	299/9163	3.3	(2.91; 3.65)	314/9492	3.3	(2.96; 3.69)
Related SAE <=28 days post dose	4/19715	<0.1	(0.01; 0.05)	2/9163	<0.1	(0.00; 0.08)	2/9492	<0.1	(0.00; 0.08)
Related SAE >28 days to 6 months post dose	2/19715	<0.1	(0.00; 0.04)	0/9163	0.0	(0.00; 0.04)	0/9492	0.0	(0.00; 0.04)
Neurological disorder SAE <=30 days post dose	12/19715	<0.1	(0.03; 0.11)	8/9163	<0.1	(0.04; 0.17)	9/9492	<0.1	(0.04; 0.18)
Neurological disorder SAE >30 days to 6 months post dose	25/19715	0.1	(0.08; 0.19)	11/9163	0.1	(0.06; 0.21)	13/9492	0.1	(0.07; 0.23)
Death within 6 months post dose	5/19715	<0.1	(0.01; 0.06)	4/9163	<0.1	(0.01; 0.11)	4/9492	<0.1	(0.01; 0.11)
Related death within 6 months post dose	0/19715	0.0	(0.00; 0.02)	0/9163	0.0	(0.00; 0.04)	0/9492	0.0	(0.00; 0.04)

n: number of subjects experiencing the endpoint
M: number of subjects with available data for the relevant endpoint
CYD dengue vaccine 5 ± 1 log10 CCID50 of serotypes 1, 2, 3 and 4
Main studies applied a D0/M6/M12 vaccine schedule
* Identified in the termination form as SAE or other AE
Contributing studies: CYD13 CYD14 CYD15 CYD22 CYD23 CYD24 CYD28 CYD30 CYD32 CYD65 CYD67 CYD71
Unsolicited non-serious AEs and ARs that occurred within the 28 days post-injection visit's time window (+14 days in most studies) were also included in the Safety Overview tables to provide a more comprehensive overview

Source: modified from 5.3.5.3 Integrated Safety Analysis Report, Table 3.12.1.1a.

When comparing the safety overview in children from 6 to 8 years old to the safety overview in children from 9 to 17 years old (after any of 3 doses of CYD dengue vaccine, regardless of baseline dengue serostatus), the CHMP considered the following:

- Similar frequencies in the 2 populations: solicited reactions, solicited systemic reactions, unsolicited AE/AR (non-serious and grade 3), unsolicited injections site AR (non-serious and grade 3), unsolicited systemic AE/AR (non-serious and grade 3), anaphylactic reaction (SMQ), allergic reactions (targeted list: non-serious and grade 3), post-vaccination dengue-like syndrome, discontinuation due to AE, serious allergic reactions (target list); related SAE (≤ 28 days and >28 days to 6 months post dose), neurological disorders SAE (≤30 days and >30 days to 6 months post dose), and related death within 6 months.

- Increase with age increase: immediate unsolicited AE and AR (all and grade 3: none in children from 6 to 8 years to several in children from 9 to 17 years), grade 3 solicited reactions (from 5.9% to 11.1%), grade 3 solicited injection site reactions (from 0.4% to 1.5%), grade 3 solicited systemic reactions (from 5.7% to 10.4%), and death within 6 months (from none to <0.1% - 5 deaths).

- Decrease with age increase: solicited injection site reactions (from 56.1% to 51.6%), SAE ≤ 28 days (from 1.3% to 0.6%) and SAE >28 days to 6 months post dose (from 5.6% to 2.8%).

The observed differences could be due to chance-finding due the differences in the number of subjects compared: children from 6 to 8 years (SafAS: 3233 subjects and RS: 768 subjects) and children from 9 to 17 years (SafAS: 19715 subjects and RS: 3666 subjects).

Overall, no major differences are observable between the reactogenicity and the safety profile in children from 6 to 8 years old and children from 9 to 17 years old (population in which the vaccine is currently licensed) after any of 3 doses of CYD dengue vaccine, regardless of baseline dengue serostatus.

Conclusion

In both age groups (6 to 8 years and 9 to 17 years), the incidence of most parameters tended to decrease with each subsequent injection in all subjects regardless of the baseline serostatus and in seropositive subjects. Overall, no major differences were observed between the 2 age groups in the reactogenicity and safety profile of the CYD dengue vaccine after each CYD dengue vaccine injection.

2.3.3. Comparison to safety overview in subjects aged 2 to 5 years

Safety Overview in Subjects Aged 2 to 5 Years

A safety overview for the Main Studies in which the CYD dengue vaccine was administered as a 3-dose schedule (injections at 6-months intervals) was presented for subjects aged 2 to 5 years, regardless of baseline dengue serostatus, after any CYD dengue vaccine, Placebo, or Control injection

Safety Overview in Subjects Aged 2 to 5 Years

Comparison between subjects aged 6 to 8 years and 2 to 5 years, regardless of baseline dengue serostatus

The CHMP considered that, after any of 3 doses of CYD dengue vaccine, regardless of baseline dengue serostatus, there was a trend toward a slightly higher incidence after any injection in the 6 to 8 years age group compared to the 2 to 5 years age group for:

- Solicited injection site reactions (56.1% vs. 52.9%, respectively). However, Grade 3 solicited injection site reactions were reported by a similar percentage of subjects in both age groups (0.4% vs. 0.2%, respectively).

- Solicited systemic reactions (67.5% vs. 59.8%, respectively). However, Grade 3 systemic reactions were reported by a similar percentage of subjects in both age groups (5.7% vs. 6.9%, respectively).

- Unsolicited non-serious ARs (3.1% vs. 1.8%). Grade 3 unsolicited non-serious ARs were reported by a low percentage of subjects after any injection in both age groups (≤ 0.2%).

A slightly lower incidence was observed after any injection in the 6 to 8 years age group compared to the 2 to 5 years age group for the unsolicited non-serious AEs (43.8% vs. 50.9%, respectively).

Overall, no major differences are observable between the reactogenicity and the safety profile in children from 6 to 8 years old and children from 2 to 5 years old after any of 3 doses of CYD dengue vaccine, regardless of baseline dengue serostatus. The incidence of SAEs within 28 days was ≤ 1.5% and the incidence of subjects discontinued due to an AE was 0.2% in both age groups.

Comparison between subjects aged 6 to 8 years and 2 to 5 years, baseline dengue seropositive

The trends observed in subjects regardless of baseline dengue serostatus tended to disappear in baseline dengue seropositive subjects. After any of 3 doses of CYD dengue vaccine, while comparing the 6 to 8

years age group to the 2 to 5 years age group (baseline dengue seropositive subjects), similar incidence were observed for :

- Solicited injection site reactions (50.2% vs. 48.4%, respectively).

- Solicited systemic reactions (57% vs. 54.8%, respectively).

- Unsolicited non-serious ARs (1.7% vs. 1.3%).

However, a clear lower incidence was observed after any injection in the 6 to 8 years age group compared to the 2 to 5 years age group for the unsolicited non-serious AEs (37.1% vs. 51.9%, respectively)

No major differences were observed in the frequencies of the other parameters, which were reported at low frequencies. For instance, the incidence of SAEs within 28 days was ≤ 1.4%, and the incidence of subjects discontinued due to an AE was 0.3% in both age groups.

Conclusion

The safety overview profile of the CYD dengue vaccine was similar in children aged 6 to 8 years and 2 to 5 years. Of note, the vast majority of results assessing the risk for HVCD and SVCD in 2 to 5 years children were inconclusive and 1 of the methods showed an increased risk of SVCD with a HR estimate above 1; therefore, precluding the indication in this age group.

2.3.4. Adverse Events of Special Interest (AESI)

2.3.4.1. Allergic/Anaphylactic reactions in children aged 6 to 8 years

No anaphylactic reactions occurred in children aged 6 to 8 years in the CYD dengue vaccine, placebo and control groups.

In the CYD dengue vaccine Group, within 7 days after injection, regardless of baseline serostatus, a total of 6 subjects out of 768 (0.8%) experienced 6 potential non-serious allergic reactions: asthma, rah, rash macular and 3 urticaria. Among these events, 2 were considered as related to the vaccine (0.3%): a Grade 1 rash after first injection and a Grade 2 urticaria after injection 2. All potential non-serious allergic reactions were either Grade 1 or Grade 2.

In the placebo (0.4%) and the control group (0.3%), there was 1 non-serious allergic reaction each (1 hypersensitivity each assessed as related).

Overall, the proportion of subjects aged 6 to 8 years who experimented a potential non-serious allergic reaction tended to remain low and stable after each subsequent injection with 0.4%, 0.1%, and 0.3% after the first, second, and third injection, respectively.

No subject experienced a serious allergic reaction in any of the 3 treatment groups.

In all studies, compared to the Main Studies, no additional anaphylactic reactions and serious allergic reactions occurred in the CYD dengue vaccine Group. One additional potential non-serious allergic reaction was reported in the CYD dengue vaccine Group in the CYD05 study: a Grade 2 asthma after the third injection. Overall, the proportion of subjects who reported at least 1 potential non-serious allergic reaction was similar in the Main Studies and All Studies sets with an incidence of 0.8% and 0.9%, respectively.

The CHMP considered that, In the safety overview in children from 9 to 17 years old (after any of 3 doses of CYD dengue vaccine, regardless of baseline dengue serostatus), there were no anaphylactic reactions,

and 0.5% of non-serious allergic reaction (targeted list) in the CYD dengue vaccine group (including 1 grade 3), 0.4% in placebo group and 0.7% in control group.

2.3.4.2. Viscerotropic and neurotropic events

Among subjects aged 6 to 8 years at enrolment (regardless of serostatus), there were 3 subjects with suspected neurotropism:

• A subject (Subject 220-00332 in CYD14) in the CYD dengue vaccine Group for whom the PT of the final diagnosis was acute disseminated encephalomyelitis. The event occurred 20 days after the first injection and lasted 14 days.

• A subject (Subject 115-00040 in CYD14) in the Placebo Group for whom the PT of the final diagnosis was seizure. The event occurred 28 days after the second placebo injection and lasted 3 days. The event was assessed as not related to study vaccination.

• A subject (Subject 004-10009 in CYD32) in the Placebo Group for whom the PT of the final diagnosis was VIIth nerve paralysis. The event occurred 20 days after the first placebo injection and lasted 128 days. The event was assessed as related to study vaccination.

Among subjects aged 6 to 8 years, no suspected viscerotropism was reported.

In conclusion, no events of viscerotropic or neurotropic disease were observed after administration of the CYD dengue vaccine in any studies.

The CHMP, as discussed above considered that subject 220-00332 presented a related SAE of acute disseminated encephalomyelitis (ADEM) in the CYD dengue vaccine group 7 days after the first study vaccination. Vaccinal and wild-type dengue virus test was negative in serum, blood, urine and cerebrospinal fluid. Therefore, a neurotropic disease with replication of the vaccinal virus in the CNS was excluded.

So far (neither from any study nor from post-marketing), no confirmed events of neurotropic disease (i.e. vaccinal virus detection in CNS) were observed after administration of the CYD dengue vaccine in any studies. Although this important potential risk remains theoretical, the MAH will continue to monitor neurotropic disease as part of its pharmacovigilance activities, as described in the RMP. Neurotropism occurring within 30 days after injection throughout trials had been defined as Adverse Events of Special Interest (AESI).

2.3.4.3. Severe dengue disease

In individual studies, SDD was defined as an AESI, i.e. as a suspected dengue case as per the Investigator judgment, regardless of severity and prior to virological confirmation with the following definition: acute febrile illnesses (temperature $\geq$ 38° C) on at least 2 consecutive days requiring hospitalization (with bed attribution), and were to be collected during the entire study period.

In the Phase III studies included the integrated safety analysis, serious/severe dengue diseases (SDDs) were collected in CYD32, CYD14, CYD15, CYD67, and CYD71 for subjects aged 9 to 17 years, and in CYD32 and CYD14 for subjects aged 6 to 8 years. SDDs were collected up to 6 months post-injection 3 in CYD32, CYD67, and CYD71, and up to 60 months post-injection 3 in CYD14 and CYD15. Due to the difference in the time period of collection, the frequency of SDDs by baseline dengue serostatus is presented by study for the 2 age groups in Table below. For CYD67 and CYD71, which evaluated the coadministration of human papillomavirus vaccine with the CYD dengue vaccine, only the sequential groups were considered in the integrated safety analysis and are presented in the Table below.

Of note, in most of these cases, the diagnosis of SDD was made at hospital admission by clinicians that were not part of the trial. Moreover, in instances where investigators were the clinicians assessing trial subjects, the assessment to determine whether they met the definition of SDD (see above) was made blinded to the group allocation of the subjects.

In individual studies, AESI of SDD included all dengue disease assessed as serious per the Investigator, either virologically-confirmed or not. However, in the present integrated/pooled analyses, it was more relevant for the Sponsor to focus specifically on severe VCD cases (as systematically assessed for severity by the IDMC) instead of SDD.

Table 19: Serious dengue disease occurring during the entire study by baseline dengue status - Safety Analysis Set

			CYD Dengue Vaccine Group				Placebo Group			
Dengue Status	**Age Group**	**Subjects experiencing at least one SDD in:**	**n/M**	**%**	**(95% CI)**	**n AESIs**	**n/M**	**%**	**(95% CI)**	**n AESIs**
Immune	**6-8 years**	**CYD14**	6/169	3.6	(1.3; 7.6)	6	9/88	10.2	(4.8;18.5)	9
		CYD32	0/22	0.0	(0.0;15.4)	0	0/3	0.0	(0.0;70.8)	0
	9-17 years	**CYD14**	5/487	1.0	(0.3; 2.4)	5	9/251	3.6	(1.7; 6.7)	9
		CYD15	8/1073	0.8	(0.3; 1.5)	10	12/512	2.3	(1.2; 4.1)	12
		CYD32	0/22	0.0	(0.0;15.4)	0	0/9	0.0	(0.0;33.6)	0
		CYD67	0/88	0.0	(0.0; 4.1)	0	NA	NA	NA	NA
		CYD71	0/151	0.0	(0.0; 2.4)	0	NA	NA	NA	NA
Non-immune	**6-8 years**	**CYD14**	5/83	6.0	(2.0;13.5)	6	1/38	2.6	(0.1;13.8)	1
		CYD32	0/35	0.0	(0.0;10.0)	0	0/8	0.0	(0.0;36.9)	0
	9-17 years	**CYD14**	5/129	3.9	(1.3; 8.8)	6	6/59	10.2	(3.8;20.8)	9
		CYD15	3/258	1.2	(0.2; 3.4)	3	0/149	0.0	(0.0; 2.4)	0
		CYD32	0/21	0.0	(0.0;16.1)	0	0/5	0.0	(0.0;52.2)	0
		CYD67	3/168	1.8	(0.4; 5.1)	3	NA	NA	NA	NA
		CYD71	0/82	0.0	(0.0; 4.4)	0	NA	NA	NA	NA
Total	**6-8 years**	**CYD14**	71/1877	3.8	(3.0; 4.7)	72	53/942	5.6	(4.2; 7.3)	56
		CYD32	0/57	0.0	(0.0; 6.3)	0	0/11	0.0	(0.0;28.5)	0
	9-17 years	**CYD14**	73/3315	2.2	(1.7; 2.8)	74	69/1657	4.2	(3.3; 5.2)	72
		CYD15	100/13915	0.7	(0.6; 0.9)	103	95/6939	1.4	(1.1; 1.7)	95
		CYD32	0/43	0.0	(0.0; 8.2)	0	0/14	0.0	(0.0;23.2)	0
		CYD67	3/256	1.2	(0.2; 3.4)	3	NA	NA	NA	NA
		CYD71	0/233	0.0	(0.0; 1.6)	0	NA	NA	NA	NA

n: number of subjects in the specified category.

n AESIs: number of serious AESIs dengue disease.

Serious dengue AESI are SAEs identified as 'dengue' by the investigator (Preferred Term of the SAE contains 'Dengue'), virologically-confirmed or not.

For study CYD67 and CYD71, only sequential vaccination with Dengue vaccine are counted in CYD Dengue Vaccine Group

NA: not applicable

5.3.5.3 Supplement 1 to the Integrated Safety Analysis Report, Table E.2.3.3 (see "Integrated Summary of Safety [ISS]" Tables – Supplement 1)

The CHMP considered that:

In the 6 to 8 years age group, all SDDs were reported in CYD14 (none in CYD32). In all subjects regardless of the baseline dengue serostatus, the frequency of SDDs tended to be slightly lower in the CYD dengue vaccine Group (3.8% - 72 SDDs) than in the Placebo Group (5.6% - 56 SDDs). When considering subjects from the immunogenicity subset, the frequency of SDDs was lower in the CYD dengue vaccine Group than in the Placebo group in seropositive subjects (3.6% versus 10.2%), and

higher in the CYD dengue vaccine Group than in the Placebo Group in seronegative subjects (6.0% versus 2.6%).

In the 9 to 17 years age group, SDDs were reported in CYD14, CYD15, and CYD67 studies.

In CYD67 study (sequential group), SDD frequency was low (0% in seropositive subjects, and 1.8% in seronegative subjects).

In CYD14 and CYD15, the frequency of SDDs in all subjects regardless of the baseline dengue serostatus, tended to be slightly lower in the CYD dengue vaccine Group than in the Placebo Group (2.2% versus 4.2% in CYD14, and 0.7% versus 1.4% in CYD15). In CYD14, the frequency of SDDs tended to be slightly lower in the CYD dengue vaccine Group than in the Placebo Group in both seropositive subjects (1.0% versus 3.6%) and seronegative subjects (3.9% versus 10.2%), among subjects from the immunogenicity subset. In CYD15, the frequency of SDDs tended to be lower in the CYD dengue vaccine Group (0.8%) than in the Placebo Group (2.3%) in seropositive subjects, and higher in the CYD dengue vaccine Group (1.2%) than in the Placebo Group (0%) in seronegative subjects.

Overall, in both treatment groups (CYD dengue vaccine or placebo), the frequency of SDDs tended to be lower in the 9 to 17 years than in the 6 to 8 years age group in seropositive subjects. The frequency of SDDs was consistently lower, in the CYD dengue vaccine Group than in the Placebo group in seropositive subjects, in the two age groups.

2.3.5. Safety during the long-term follow-up

2.3.5.1. SAEs and Deaths During Long-term Follow-ups

SAEs and deaths that occurred during LTFU in CYD05, CYD22, CYD28, CYD57, CYD14, CYD15, and CYD65 are presented for subjects aged 6 to 60 years in Integrated Safety Analysis Report, Listings Part 2, [Listing 3.32.2]. The collection of SAEs after 6 months post any injection differed by study:

- In CYD05, SAEs and deaths were collected from D0 to M60 post-injection 3.
- In CYD22 and CYD28, only related SAEs and deaths were collected up to 48 months postinjection 3.
- In CYD57, only related SAEs and deaths were collected from 13 to 60 months postinjection 3.
- In CYD14 and CYD15, all SAEs were collected during the entire duration of the study, i.e. up to 60 months post-injection 3.
- In CYD65, for the primary series, all SAEs were collected from D0 until the administration of the CYD dengue vaccine booster injection.

Table 20: All SAEs reported in at least 0.1% in long term follow-up period after any CYD dengue vaccine dose or placebo - Subjects 6-8 - SafAS CYD14

		CYD dengue vaccine				Placebo			
		All SAEs				All SAEs			
Baseline dengue status	**Subjects experiencing at least one:**	**n/N**	**%**	**(95% CI)**	**n SAEs**	**n/N**	**%**	**(95% CI)**	**n SAEs**
Non-immune	**SAE**	8/83	9.6	(4.25; 18.11)	8	2/38	5.3	(0.64; 17.75)	2
	Infections and infestations	6/83	7.2	(2.70; 15.07)	6	1/38	2.6	(0.07; 13.81)	1
	Dengue fever	3/83	3.6	(0.75; 10.20)	3	1/38	2.6	(0.07; 13.81)	1

		CYD dengue vaccine				Placebo			
		All SAEs				All SAEs			
Baseline dengue status	**Subjects experiencing at least one:**	**n/N**	**%**	**(95% CI)**	**n SAEs**	**n/N**	**%**	**(95% CI)**	**n SAEs**
	Dengue haemorrhagic fever	1/83	1.2	(0.03; 6.53)	1	0/38	0.0	(0.00; 9.25)	0
	Influenza	1/83	1.2	(0.03; 6.53)	1	0/38	0.0	(0.00; 9.25)	0
	Upper respiratory tract infection	1/83	1.2	(0.03; 6.53)	1	0/38	0.0	(0.00; 9.25)	0
	Immune system disorders	1/83	1.2	(0.03; 6.53)	1	0/38	0.0	(0.00; 9.25)	0
	Anaphylactic reaction	1/83	1.2	(0.03; 6.53)	1	0/38	0.0	(0.00; 9.25)	0
	Injury, poisoning and procedural complications	1/83	1.2	(0.03; 6.53)	1	0/38	0.0	(0.00; 9.25)	0
	Adverse event following immunisation	1/83	1.2	(0.03; 6.53)	1	0/38	0.0	(0.00; 9.25)	0
Immune	**SAE**	16/169	9.5	(5.51; 14.92)	19	12/88	13.6	(7.25; 22.61)	17
	Infections and infestations	12/169	7.1	(3.72; 12.07)	13	11/88	12.5	(6.41; 21.27)	15
	Dengue fever	4/169	2.4	(0.65; 5.95)	4	2/88	2.3	(0.28; 7.97)	2
	Gastroenteritis viral	2/169	1.2	(0.14; 4.21)	2	0/88	0.0	(0.00; 4.11)	0
	Tonsillitis	2/169	1.2	(0.14; 4.21)	2	0/88	0.0	(0.00; 4.11)	0
	Appendicitis	1/169	0.6	(0.01; 3.25)	1	0/88	0.0	(0.00; 4.11)	0
	Dengue haemorrhagic fever	1/169	0.6	(0.01; 3.25)	1	5/88	5.7	(1.87; 12.76)	5
	Gastroenteritis	1/169	0.6	(0.01; 3.25)	1	0/88	0.0	(0.00; 4.11)	0
	Influenza	1/169	0.6	(0.01; 3.25)	1	0/88	0.0	(0.00; 4.11)	0
	Pneumonia viral	1/169	0.6	(0.01; 3.25)	1	0/88	0.0	(0.00; 4.11)	0
	Injury, poisoning and procedural complications	3/169	1.8	(0.37; 5.10)	3	0/88	0.0	(0.00; 4.11)	0
	Road traffic accident	2/169	1.2	(0.14; 4.21)	2	0/88	0.0	(0.00; 4.11)	0
	Sports injury	1/169	0.6	(0.01; 3.25)	1	0/88	0.0	(0.00; 4.11)	0
	Gastrointestinal disorders	1/169	0.6	(0.01; 3.25)	1	2/88	2.3	(0.28; 7.97)	2
	Enteritis	1/169	0.6	(0.01; 3.25)	1	0/88	0.0	(0.00; 4.11)	0
	Renal and urinary disorders	1/169	0.6	(0.01; 3.25)	1	0/88	0.0	(0.00; 4.11)	0
	Glomerulonephritis acute	1/169	0.6	(0.01; 3.25)	1	0/88	0.0	(0.00; 4.11)	0
	Respiratory, thoracic and mediastinal disorders	1/169	0.6	(0.01; 3.25)	1	0/88	0.0	(0.00; 4.11)	0
	Asthma	1/169	0.6	(0.01; 3.25)	1	0/88	0.0	(0.00; 4.11)	0
Total	**SAE**	172/1877	9.2	(7.90; 10.56)	200	102/942	10.8	(8.92; 12.99)	130
	Infections and infestations	126/1877	6.7	(5.62; 7.94)	134	75/942	8.0	(6.31; 9.88)	91
	Dengue fever	33/1877	1.8	(1.21; 2.46)	33	20/942	2.1	(1.30; 3.26)	20
	Dengue haemorrhagic fever	29/1877	1.5	(1.04; 2.21)	29	20/942	2.1	(1.30; 3.26)	20
	Pharyngitis	9/1877	0.5	(0.22; 0.91)	12	6/942	0.6	(0.23; 1.38)	6
	Tonsillitis	8/1877	0.4	(0.18; 0.84)	8	0/942	0.0	(0.00; 0.39)	0
	Appendicitis	5/1877	0.3	(0.09; 0.62)	5	2/942	0.2	(0.03; 0.76)	2
	Typhoid fever	5/1877	0.3	(0.09; 0.62)	5	1/942	0.1	(0.00; 0.59)	1
	Pneumonia	4/1877	0.2	(0.06; 0.54)	5	3/942	0.3	(0.07; 0.93)	3
	Viral infection	4/1877	0.2	(0.06; 0.54)	4	9/942	1.0	(0.44; 1.81)	9

		CYD dengue vaccine				Placebo			
		All SAEs				All SAEs			
Baseline dengue status	**Subjects experiencing at least one:**	**n/N**	**%**	**(95% CI)**	**n SAEs**	**n/N**	**%**	**(95% CI)**	**n SAEs**
	Amoebiasis	3/1877	0.2	(0.03; 0.47)	3	1/942	0.1	(0.00; 0.59)	1
	Bronchitis	3/1877	0.2	(0.03; 0.47)	3	0/942	0.0	(0.00; 0.39)	0
	Gastrointestinal infection	3/1877	0.2	(0.03; 0.47)	3	3/942	0.3	(0.07; 0.93)	3
	Influenza	3/1877	0.2	(0.03; 0.47)	3	0/942	0.0	(0.00; 0.39)	0
	Urinary tract infection	3/1877	0.2	(0.03; 0.47)	3	2/942	0.2	(0.03; 0.76)	4
	Gastroenteritis	2/1877	0.1	(0.01; 0.38)	2	3/942	0.3	(0.07; 0.93)	3
	Gastroenteritis viral	2/1877	0.1	(0.01; 0.38)	2	0/942	0.0	(0.00; 0.39)	0
	Upper respiratory tract infection	2/1877	0.1	(0.01; 0.38)	2	2/942	0.2	(0.03; 0.76)	2
	Injury, poisoning and procedural complications	29/1877	1.5	(1.04; 2.21)	31	12/942	1.3	(0.66; 2.21)	12
	Road traffic accident	6/1877	0.3	(0.12; 0.69)	7	3/942	0.3	(0.07; 0.93)	3
	Fall	5/1877	0.3	(0.09; 0.62)	5	1/942	0.1	(0.00; 0.59)	1
	Arthropod bite	2/1877	0.1	(0.01; 0.38)	2	0/942	0.0	(0.00; 0.39)	0
	Head injury	2/1877	0.1	(0.01; 0.38)	2	1/942	0.1	(0.00; 0.59)	1
	Sports injury	2/1877	0.1	(0.01; 0.38)	2	0/942	0.0	(0.00; 0.39)	0
	Gastrointestinal disorders	14/1877	0.7	(0.41; 1.25)	14	11/942	1.2	(0.58; 2.08)	12
	Food poisoning	4/1877	0.2	(0.06; 0.54)	4	0/942	0.0	(0.00; 0.39)	0
	Gastritis	3/1877	0.2	(0.03; 0.47)	3	3/942	0.3	(0.07; 0.93)	3
	Colitis	2/1877	0.1	(0.01; 0.38)	2	0/942	0.0	(0.00; 0.39)	0
	Enteritis	2/1877	0.1	(0.01; 0.38)	2	1/942	0.1	(0.00; 0.59)	2
	Gastrointestinal disorder	2/1877	0.1	(0.01; 0.38)	2	2/942	0.2	(0.03; 0.76)	2
	Renal and urinary disorders	5/1877	0.3	(0.09; 0.62)	6	2/942	0.2	(0.03; 0.76)	4
	Post streptococcal glomerulonephritis	2/1877	0.1	(0.01; 0.38)	2	1/942	0.1	(0.00; 0.59)	1
	Immune system disorders	3/1877	0.2	(0.03; 0.47)	4	1/942	0.1	(0.00; 0.59)	1
	Anaphylactic reaction	3/1877	0.2	(0.03; 0.47)	3	0/942	0.0	(0.00; 0.39)	0
	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2/1877	0.1	(0.01; 0.38)	2	0/942	0.0	(0.00; 0.39)	0
	Respiratory, thoracic and mediastinal disorders	2/1877	0.1	(0.01; 0.38)	2	3/942	0.3	(0.07; 0.93)	3

n: number of subjects experiencing the endpoint. n SAEs: number of SAEs
N: total number of subjects per dose
Long-term follow up starts 6 months after last dose until the end of the study
CYD dengue vaccine 5 ± 1 log10 CCID50 of serotypes 1, 2, 3 and 4
Contributing studies: CYD14

The CHMP noted that:

In subjects aged 6 to 8 years at enrollment, 174 subjects experienced a total of 202 SAEs during LTFU after any CYD dengue vaccine dose. Except for 2 subjects (1 from CYD28 and 1 from CYD23/57), all subjects were enrolled in CYD14. The SAE reported in CYD23/57 was the only fatal one in this age group (PT: gun shot wound) in the CYD dengue vaccine Group. After any Placebo dose, 103 subjects experienced a total of 131 SAEs during LTFU. Except for 1 subject of CYD23/57, all subjects were enrolled

in CYD14. In CYD14, the frequency of LTFU SAEs in all subjects aged 6 to 8 years was 9.2% in the CYD dengue vaccine Group and 10.8% in the Placebo Group (regardless of baseline dengue serostatus). No related SAEs were reported during the LTFU in any groups of these studies.

In the CYD dengue vaccine Group (in CYD14, regardless of baseline dengue serostatus), SAEs were mostly reported in SOCs Infections and infestations (6.7%), Injury, poisoning and procedural complications (1.5%), Gastrointestinal disorders (0.7%). Similar frequencies and same trends were reported in dengue seropositive subjects (SAE frequency of 9.5% and respectively 7.1%, 1.8% and 0.6% for the SOC most frequently reported).

In subjects aged 9 to 17 years at enrollment, LTFU SAEs were reported with a frequency of 10.3% in the CYD dengue vaccine Group (in CYD14+CYD15 , regardless of baseline dengue serostatus) (compared to 10.9% in placebo group). In the CYD dengue vaccine Group, SAEs were mostly reported in SOCs Infections and infestations (4.4%), Injury, poisoning and procedural complications (2.1%), Pregnancy, puerperium and perinatal conditions (1.8%), and Gastrointestinal disorders (0.5%). Similar frequencies and same trends were reported in dengue seropositive subjects (SAE frequency of 11.8% and respectively 4.5%, 3.5%, 1.8% and 0.6% for the SOC most frequently reported).

LTFU SAEs were mostly reported in the same SOCs for both age groups; however, some differences were observed:

- SAEs in the following SOCs were slightly more frequently reported in subjects aged 9 to 17 years than in subjects aged 6 to 8 years (regardless of baseline dengue serostatus): Nervous system disorders (0.4%), Respiratory, thoracic and mediastinal disorders (0.3%) in subjects aged 9 to 17 years, and <0.1% for both SOCs in subjects aged 6 to 8 years .

- SAEs in the following SOCs were slightly more frequently reported in subjects aged 6 to 8 years compared than in subjects 9 to 17 years (regardless of baseline dengue serostatus): Infections and infestations (6.7% versus 4.4%), Renal and urinary disorders (0.3 % versus 0.1%).

- The following SOCs (≥0.1%) were reported only in subjects aged 9 to 17 years (regardless of baseline dengue serostatus) but with SAEs frequency mostly < 0.1%: Pregnancy, puerperium and perinatal conditions (1.8%), Reproductive system and breast disorders (0.3%), Psychiatric disorders (0.4%), Hepatobiliary disorders (0.2%), Social circumstances (0.2%), Blood and lymphatic system disorders (0.1%).

- No SOC were only reported in subjects aged 6 to 8 years (regardless of baseline dengue serostatus).

In subjects aged 6 years and above, regardless of baseline dengue serostatus, the following number of deaths was reported during the LTFU: 0 death in CYD05, 1 death (Control Group) in CYD22, 3 deaths (CYD dengue vaccine Group) in CYD28, 5 deaths (3 in the CYD dengue vaccine Group, and 2 in the Placebo Group) in CYD57, 9 deaths (7 in the CYD dengue vaccine Group and 2 in the Placebo Group) in CYD14, 63 deaths (40 in the CYD dengue vaccine Group and 23 in the Placebo Group) in CYD15, and no reported deaths in CYD65. No related deaths were reported during the LTFU of any of these studies.

A large proportion of the fatal cases during LTFU originated from violence-related deaths (firearm/gunshot deaths) and accidents in general, particularly traffic accidents. Apart from these, some isolated medical conditions leading to death in LTFU have been reported, often linked to an obvious alternative explanation, with long latency to last administration and lack of any plausible causal association with CYD dengue vaccine. Taken together, the deaths in LTFU reported (all assessed as not related cases) do not raise concern on the vaccine safety.

From these described deaths during the LTFU period, 3 deaths were reported in the 6 to 8 years age group: one in the CYD dengue vaccine Group (PT: gun shot wound in CYD23/57), and 2 in the Placebo Group (1 in CYD14 and 1 in CYD57).

2.3.6. Laboratory findings

No new clinical laboratory parameters assessments were performed since the CYD dengue vaccine file was submitted or last updated.

2.3.7. Safety in special populations

Although the safety database was updated with data from recently completed studies, no additional assessments of the potential impact of intrinsic and extrinsic factors were performed since the CYD dengue vaccine file was submitted or last updated.

The dengue status at baseline is discussed independently in the previous sections.

2.3.8. Safety related to drug-drug interactions and other interactions

No new evaluation of interactions between the CYD dengue vaccine and other vaccines was performed since the file was submitted or last updated.

Post marketing experience

The CYD dengue vaccine was first registered on 08 December 2015 in Mexico, and has been registered as of 7 March 2020 in 21 countries, including the US, and in the European Economic Area, with commercial use in 10 countries (Brazil, Costa Rica, El Salvador, Guatemala, Indonesia, Mexico, Paraguay, Peru, Singapore, and Thailand).

The CYD dengue vaccine has been indicated for individuals of 9 years or age older. However, vaccination with the CYD dengue vaccine has occurred out of this indicated age. In DNG15, an ongoing post-authorization and non-interventional safety study under real-world conditions in AP and LatAm, participants were vaccinated before their enrolment in the study, reflecting the real-world use of the vaccine, in routine medical care in each study country. As of 07 December 2019, a total of 12 616 participants have been enrolled in three countries and have received at least one vaccine injection. 2308 participants have been enrolled in Brazil; 88 participants have been enrolled in Mexico and 10 220 participants have been enrolled in the Philippines. The average age overall was 14.5 years, ranging from 7 to 73 years. Notably, 96 participants in these countries were younger than the age of indication at first dose: 4 were aged 7 years and 92 were aged 8 years. Of the 96 subjects, 5 were in Brazil, 4 were in Mexico, and 91 were in the Philippines. No safety signal has been identified based on safety data reported in individuals from 6 to 8 years of age who have received at least one dose of the CYD dengue vaccine.

Cumulative post-approval exposure to CYD dengue vaccine (from 01 December 2015 to 29 February 2020) was estimated to be 2 909 464. Assuming that patients may have received between 1 and 3 doses in accordance with the recommended schedule, the estimated cumulative number of patients who received CYD dengue vaccine is between 969 821 and 2 909 464.

It is to be noted that the vast majority of the doses of CYD dengue vaccine were used during public vaccination campaigns in the Philippines and in Parana state of Brazil, where 2.3 M doses were distributed and at least 1.47 M doses administered across the 2 programs.

No safety signal has been confirmed from post-marketing use of the vaccine as of 7 March 2020.

The most frequently reported AEs are consistent with current label information.

Discussion on clinical safety

Current safety profile of the CYD dengue vaccine

In subjects 9 to 45 years of age, the most frequently reported reactions whatever the dengue serostatus prior to vaccination, were headache (54%), injection site pain (49%), malaise (44%), myalgia (43%), asthenia (34%), and fever (16%). Adverse reactions occur within 3 days following vaccination except fever which appears within 14 days after the injection. The adverse reactions were usually mild to moderate in severity and of short duration (0 to 3 days). Systemic adverse reactions tended to be less frequent after the second and third injections of Dengvaxia as compared to the first injection. Allergic including anaphylactic reactions have been reported very rarely. Overall, the same adverse reactions but at lower frequencies were observed in dengue seropositive subjects.

Exposure to Drug

In the 17 studies using the final formulation and a 3-dose vaccination schedule D0/M6/M12 that provided the main data to support the Application (SafAS), 24 733 subjects aged 6 to 60 years received at least 1 injection of the CYD dengue vaccine, including 3233 children aged 6 to 8 years, 19 715 children / adolescents aged 9 to 17 years, 1492 adults aged 18 to 45 years, and 293 adults aged 46 to 60 years.

The Reactogenicity Subset for the 3-dose schedule included a total of 6219 subjects aged 6 to 60 years, including 768 children aged 6 to 8 years, 3666 children / adolescents aged 9 to 17 years, 1492 adults aged 18 to 45 years, and 293 adults aged 46 to 60 years.

Demographics

In the included 3233 children aged 6 to 8 years, the distribution between males and females was similar. The mean age of subjects at enrolment for the combined regions was 7.0 years. There were no subjects aged 6 to 8 years from the non-endemic region.
The majority of the treated children aged 6 to 8 years (3179 children of the 3233) were from endemic Asia Pacific (AP), and all the subjects who provided ethnicity data were Asian (i.e. no ethnic origin data collected for the 54 children in the LatAm region). The representability of the included population is questioned, in particular concerning the extrapolation of one epidemiological context to another in the context of the theoretical risk of cross-enhancement of other flaviviruses.

Among subjects from the combined regions with an available dengue serostatus (529 out of 3233 subjects), 294 were baseline seropositive (55.6%).

Safety Overview in Subjects 6 to 8 Years

Overall, the reactogenicity and safety profile of the CYD dengue vaccine in terms of incidence, intensity, and nature of events in subjects regardless of dengue baseline serostatus was generally similar to that reported after placebo or control injections. A trend toward a slightly higher incidence of solicited systemic reactions in the CYD dengue vaccine Group was observed. Overall, a similar reactogenicity and safety profile was observed vs placebo or control in seropositive subjects; however, a trend toward a slightly higher incidence of solicited injection site reactions in the CYD dengue vaccine Group was also observed.

Solicited injection site reactions, solicited systemic reactions and unsolicited non-serious AE (mainly systemic) were observed at a lower frequencies in dengue seropositive subjects compared to all subjects regardless of baseline dengue serostatus.

The incidence of solicited systemic reactions and unsolicited non-serious AEs (mainly systemic) tended to decrease with subsequent injections.

Overall, no major differences are observable between the reactogenicity and the safety profile in children from 6 to 8 years old and children from 9 to 17 years old (population in which the vaccine is currently licensed) after any of 3 doses of CYD dengue vaccine and after each CYD dengue vaccine dose, regardless of baseline dengue serostatus and in baseline dengue seropositive.

Immediate AEs

In subjects aged 6 to 8 years regardless of baseline dengue serostatus, no immediate unsolicited AEs were reported in any of the 3 treatment groups.

Solicited Injection Site Reactions

In the CYD dengue vaccine Group regardless of baseline dengue serostatus, the most frequent solicited injection site reaction was injection site pain (51.4% of subjects); erythema (21.7%) and swelling (16.2%) were less frequently reported.

- Most solicited injection site reactions were Grade 1, occurred within 3 days after injection and had short duration (1 and 3 days).
- For all solicited injection site reactions, the maximum intensity, time to onset, and number of days of occurrence were similar in the CYD dengue vaccine, Placebo, and Control Groups.
- The incidence of each solicited injection site reaction tended to be similar after each injection.

The proportion of subjects reporting solicited injection site reactions after any injection tended to decrease as subjects' age increased with 56.1% in subjects aged 6 to 8 years, 51.6% in subjects aged 9 to 17 years, 45.4% in subjects aged 18 to 45 years, and 38.7% in subjects aged 46 to 60 years (Cf. submitted clinical safety summary).

In dengue seropositive subjects, all solicited injection site reactions (50.2%), pain (46.1%), erythema (14.3%) and swelling (12.7%) were observed at a lower frequencies compared to all subjects regardless of baseline dengue serostatus.

Solicited Systemic Reactions

In the CYD dengue vaccine Group regardless of baseline dengue serostatus, the most frequent solicited systemic reaction within 14 days after any CYD dengue vaccine injection was headache (51.5%). Malaise (44.2%) and myalgia (40.1%) were also frequently reported. The incidence of asthenia and fever were lower (32.8% and 19.6% respectively).

- Most solicited systemic reactions were Grade 1, occurred within 3 days after injection (except for fever, which appeared throughout the solicited period) and had short duration (1 and 3 days of occurrence).
- Myalgia in particular has a higher incidence in the CYD dengue vaccine group (40.1%) compared to PBO (34.5%) and control group (34.6%). Malaise has also a slightly higher incidence in the CYD dengue vaccine group (44.2% vs. 39.2% vs. 38.6%, respectively). The 3 other types of solicited systemic reactions were reported with similar frequencies in each group: headache (51.5%, 48.9%, 47.8%, respectively), asthenia (32.8% vs. 32.4% vs. 29.2%), and fever (19.6%, 18.7%, and 15.7%, respectively).

- For all solicited systemic reactions, the maximum intensity, time to onset, and number of days of occurrence were similar in the CYD dengue vaccine, Placebo, and Control Groups.
- The incidence of all solicited systemic reactions tended to decrease after each injection of vaccine.

The proportion of subjects reporting solicited systemic reactions was similar across all age groups with 67.5% in subjects aged 6 to 8 years, 65.5% in subjects aged 9 to 17 years, 63.7% in subjects aged 18 to 45 years, and 65.4% in subjects aged 46 to 60 years (Cf. submitted clinical safety summary).

In dengue seropositive subjects, solicited systemic reactions (57%), headache (42.5%), malaise (34.9%), myalgia (32.9%), asthenia (24.3%) and fever (19.1%) were observed at a lower frequencies compared to all subjects regardless of baseline dengue serostatus.

Unsolicited Non-Serious AEs and ARs

The most frequently reported unsolicited non-serious ARs after any CYD dengue vaccine injection regardless of baseline dengue serostatus were vomiting (0.9%), injection site haemorrhage (0.4%), injection site induration (0.4%), decreased appetite (0.4%), and injection site bruising (0.3%).

No clusters of ARs were observed in any of the age groups. There was only 1 Grade 3 unsolicited non-serious ARs (vomiting). Most unsolicited non-serious AEs and ARs were of Grade 1 and resolved spontaneously or with a medication within 7 days of onset or less. In addition to the intensity grading, all ARs were reviewed for clinical relevance and no concern was raised in subjects who received the CYD dengue vaccine.

After any dose, the proportion of subjects reporting at least one unsolicited AE tended to be similar across the different age groups with 43.8% in subjects aged 6 to 8 years, 40.8% in subjects aged 9 to 17 years, 39.1% in subjects aged 18 to 45 years, and 50.5% in subjects aged 46 to 60 years (Cf. submitted clinical safety summary).

The proportion of subjects reporting at least one unsolicited non-serious ARs tended to be higher in older subjects with 3.1% in subjects aged 6 to 8 years, 2.2% in subjects aged 9 to 17 years, 8.9% in subjects aged 18 to 45 years, and 17.4% in subjects aged 46 to 60 years (Cf. submitted clinical safety summary).

Deaths, SAEs, and Discontinuation due to AEs

Deaths

No death was reported in the CYD dengue vaccine Group within 6 months after any injection in the Main Studies.

SAEs within 28 days after any injection

The most frequently reported SAEs after any CYD dengue vaccine injection regardless of baseline dengue serostatus were in the following SOC: infections and infestations (0.6%: including 0.2% gastroenteritis), injury, poisoning and procedural complications (0.2%) and gastrointestinal disorders (0.1%).

No cluster in terms of nature and frequency was observed. When considering each injection, there was a trend toward a decrease incidence of SAEs within 28 days with subsequent injections.

After any dose, the proportion of subjects reporting at least one SAE tended to be similar across the different age groups with 1.3% in subjects aged 6 to 8 years, 0.6% in subjects aged 9 to 17 years, 0.7% in subjects aged 18 to 45 years, and 2% in subjects aged 46 to 60 years (Cf. submitted clinical safety summary).

After any dose, related SAEs were reported in 1 out of 3233 subjects aged 6 to 8 years (acute disseminated encephalomyelitis - <0.1%), 4 out of 19 715 subjects aged 9 to 17 years (urticaria, asthma, acute polyneuropathy, and tension headache - <0.1%), and 2 out of 293 subjects aged 46 to 60 years (polymyalgia rheumatica and headache – 0.7%). No related SAEs within 28 days were reported in adults aged 18 to 45 years.

In dengue seropositive subjects, a similar frequency of SAE was observed (1.4%).

SAEs after 28 days and up to 6 months after any injection

The most frequently reported SAEs after any CYD dengue vaccine injection regardless of baseline dengue serostatus were in the following SOC: infections and infestations (3.6%: including 0.5% dengue fever, 0.5% pharyngitis, 0.4% bronchitis, 0.4% gastroenteritis, 0.2% cellulitis, 0.2% pharyngotonsillitis, 0.2% tonsillitis and 0.2% viral infection), injury, poisoning and procedural complications (0.7%), gastrointestinal disorders (1%: including 0.6% gastritis and 0.1% food poisoning), and nervous system disorders (0.1%).

No cluster in terms of nature and frequency was observed. The incidence of SAEs tended to be similar after each injection.

No SAEs were assessed as related to the study vaccine by the Investigator between 28 days and 6 months after any injection in any of the groups.

After any dose, the proportion of subjects reporting at least one SAE tended to be similar across the different age groups with 5.6% in subjects aged 6 to 8 years, 2.8% in subjects aged 9 to 17 years, 2.8% in subjects aged 18 to 45 years, and 4.4% in subjects aged 46 to 60 years (Cf. submitted clinical safety summary).

Related SAEs were reported in 2 out of 19 715 subjects aged 9 to 17 years (dengue fever and dengue hemorrhagic fever - <0.1%) and 1 out 1492 subjects aged 18 to 45 years (blighted ovum - <0.1%). No related SAEs after 28 days and up to 6 months after any injection were reported in subjects aged 6 to 8 and 46 to 60 years.

In dengue seropositive subjects, a similar frequency of SAE was observed (5.8%).

Discontinuation due to an AE

In the CYD dengue vaccine Group, 4 subjects discontinued due to non-serious AEs (2 urticaria, illness after vaccination, and generalized itching rash) and 4 due to SAEs (rheumatic heart disease, acute disseminated encephalomyelitis, ischemic stroke, and nephrotic syndrome; only acute disseminated encephalomyelitis was assessed as related to the study vaccine).

After any dose, the proportion of subjects in the CYD dengue vaccine Group that discontinued from their study due to an AE tended to be higher in older subjects with 0.2% in subjects aged 6 to 8 years, 0.4% in subjects aged 9 to 17 years, 1.2% in subjects aged 18 to 45 years, and 2.4% in subjects aged 46 to 60 years (Cf. submitted clinical safety summary).

Dengue-like syndrome

Combination of events that were identified as potential post-vaccination dengue-like syndrome by an algorithm in the pooled/integrated analysis was not reported in subjects aged 6 to 8 years, but were reported in 3 subjects in the CYD dengue vaccine Group (2 aged 9 to 17 years out of 19 715 subjects, and 1 aged 18 to 45 years out of 1492 subjects). No safety concerns were observed in any of them.

Adverse Events of Special Interest

The analysis of AESIs showed no concerns in terms of allergic reactions, as no anaphylactic reactions were retrieved by the SMQ algorithm in subjects aged 6 to 8 years.

The proportion of subjects aged 6 to 8 years who reported potential non-serious allergic reactions was low and similar between the CYD dengue vaccine, Placebo, and Control Groups with 0.8%, 0.4%, and 0.3% of subjects, respectively.

- The proportion of subjects who reported Grade 3 potential non-serious allergic reactions was also low and similar between the CYD dengue vaccine, Placebo, and Control Groups with 0.3%, 0.4%, and 0.3% of subjects, respectively.
- No serious allergic reactions were reported in subjects aged 6 to 8 years

After any dose, the proportion of subjects reporting at least one SAE tended to be similar across the different age groups with 0.8% in subjects aged 6 to 8 years, 0.5% in subjects aged 9 to 17 years, 1.2% in subjects aged 18 to 45 years, and 1% in subjects aged 46 to 60 years (Cf. submitted clinical safety summary).

No events of viscerotropic disease were observed after administration of the CYD dengue vaccine in subjects aged 6 to 60 years. No events of neurotropic disease were observed after administration of the CYD dengue vaccine in subjects aged 8 to 60 years. One related SAE of acute disseminated encephalomyelitis happened in the subjects aged from 6 to 8 years in the CYD dengue vaccine group 7 days after the first study vaccination. Vaccinal and wild-type dengue virus test was negative in serum, blood, urine and cerebrospinal fluid. Therefore, a neurotropic disease with replication of the vaccinal virus in the CNS was excluded.

So far (neither from any study nor from post-marketing), no confirmed events of viscerotropic or neurotropic disease (i.e. vaccinal virus detection in CNS) were observed after administration of the CYD dengue vaccine in any studies. Although these important potential risks remain theoretical, the MAH will continue to monitor them as part of its pharmacovigilance activities, as described in the RMP (YF vaccine-associated viscerotropic / neurotropic disease are important potential risks). Neurotropism occurring within 30 days after injection throughout trials had been defined as Adverse Events of Special Interest (AESI).

Overall, in both treatment groups (CYD dengue vaccine or placebo), the frequency of Serious dengue disease events (SDDs) tended to be lower in the 9 to 17 years than in the 6 to 8 years age group in seropositive subjects. The frequency of SDDs was consistently lower, in the CYD dengue vaccine Group than in the Placebo group in seropositive subjects, in the two age groups. Risk of SDD due to waning protection against dengue disease over time is an important potential risk in the RMP.

Safety During the LTFU

SAEs

Overall, in children from 6 to 8 year old, during the long-term safety follow-up (reported after 6 months post any injection in the CYD dengue vaccine Group to approximatively 4.5 years), there were a similar SAE incidence in CYD dengue vaccine and placebo groups, and no SAEs were assessed as related to the study vaccine. No deaths were linked to dengue cases (only 1 death after CYD dengue vaccination due to gunshot).

HVCD – SDD in non-efficacy studies

No cases were reported in subjects aged 6 to 8 years.

Relative risks of HVCD and SVCD over the entire study and by period

Data are consistent with efficacy rather than with a safety issue. The data are discussed in the efficacy section.

Conclusions on clinical safety

The safety profile of the CYD dengue vaccine in subjects 6 to 8 years of age is very similar to the safety profile in subjects 9 to 45 years of age. The most frequently reported reactions, whatever the dengue serostatus prior to vaccination, were headache (52%), injection site pain (51%), malaise (44%), myalgia (40%), asthenia (33%), erythema (22%) and fever (20%). Adverse reactions occurred within 3 days following vaccination except fever which appears within 14 days after the injection. The adverse reactions were usually mild to moderate in severity and of short duration (0 to 3 days). Systemic adverse reactions tended to be less frequent after the second and third injections of Dengvaxia as compared to the first injection. Allergic including anaphylactic reactions have been reported very rarely. Overall, the same adverse reactions but at lower frequencies were observed in dengue seropositive subjects compared to the overall population irrespective of serostatus.

PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.4. Clinical immunogenicity

2.4.1. Introduction

Clinical immunogenicity in subjects aged 6 to 8 years is presented along with that in 2 to 5 and 9 to 17 years to offer some perspective on the available data.

Twelves clinical studies contributed to the immunogenicity results in subjects aged 2 to 5, 6 to 8, and 9 to 17 years:

• 2 large-scale pivotal efficacy studies: CYD14 and CYD15

• 10 supportive studies: 6 Phase II (CYD13, CYD22, CYD24, CYD28, CYD30, CYD65 [intermediate results]), 1 Phase IIb (CYD23), 1 Phase III (CYD32) and 2 Phase IIIb (CYD71 and CYD67)

The design and objectives of studies are summarized in the Tables below.

Table 21. Overview of studies assessing clinical immunogenicity and efficacy (studies recently completed or having recently achieved a milestone)

Study Identifier	Location of Study Report	Main Objectives of the Study	Study design	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Countries; Endemic / Non-endemic Area; Trial Period (FVFS – LVLS*)	Healthy Subjects or Diagnosis of Patients	Study Status; Type of Report
CYD14	5.3.5.1	- Vaccine efficacy against virologically-confirmed symptomatic dengue cases post-Dose 3 - Safety throughout the trial and descriptive reactogenicity (injection site and systemic) after each injection, in a subset of subjects. - Descriptive dengue humoral immune response, after the 2nd and 3rd injection, in a subset of subjects. - 5-year post-injection 3 follow-up: safety, detection of confirmed hospitalized dengue cases and antibody persistence in a subset of subjects.	Phase III, randomized, placebo-controlled, blind-observer, multicenter trial.	CYD dengue vaccine (~5 log10CCID50/ serotype 1, 2, 3, 4) Group 1: CYD dengue vaccine at D0, M6 and M12. Group 2: Placebo (NaCl 0.9%) at D0, M6 and M12. 0.5 mL/ injection. Subcutaneous injection.	Randomized: 10,275 - Group 1: 6851 - Group 2: 3424	Indonesia, Malaysia, Thailand, the Philippines, Viet Nam Endemic areas 03 Jun 2011 to 21 Nov 2017 (including a 5-year post-injection 3 follow-up)	Healthy subjects 2–14 years	Completed Final CSR
CYD15	5.3.5.1	- Vaccine efficacy against virologically-confirmed dengue cases post-Dose 3. - Safety throughout the trial and descriptive reactogenicity (injection site and systemic) after each injection, in a subset of subjects. - Descriptive dengue humoral immune response, after the 2nd and 3rd injection, in a subset of subjects. - 5-year post-injection 3 follow-up: safety, detection of confirmed hospitalized dengue cases and antibody persistence in a subset of subjects.	Phase III, randomized, placebo-controlled, blind-observer, multicenter trial.	CYD dengue vaccine (~5 log10CCID50/ serotype 1, 2, 3, 4) Group 1: CYD dengue vaccine at D0, M6 and M12. Group 2: Placebo (NaCl 0.9%) at D0, M6 and M12. 0.5 mL/ dose. Subcutaneous injection.	Randomized: 20,869 - Group 1: 13,920 - Group 2: 6949	Brazil, Colombia, Honduras, Mexico, Puerto Rico Endemic area 08 Jun 2011 to 05 Mar 2018 (including a 5-year post-injection 3 follow-up)	Healthy subjects 9–16 years	Completed Final CSR

Study Identifier	Location of Study Report	Main Objectives of the Study	Study design	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Countries; Endemic / Non-endemic Area; Trial Period (FVFS – LVLS*)	Healthy Subjects or Diagnosis of Patients	Study Status; Type of Report
CYD65	5.3.4.1	- Non-Inferiority (NI) of the dengue humoral immune response to each dengue serotype after a 2-dose schedule compared to a 3-dose schedule in baseline seropositive subjects, 28 days / 1 year after last injection - NI of the dengue humoral immune response to each dengue serotype after a booster dose compared to the last dose of a 3-dose schedule in baseline seropositive subjects - Descriptive dengue humoral immune response to each dengue serotype after the last injection of a 1-, 2-, and 3-dose schedule, 28 days / 1 year after last injection - Safety throughout the trial and descriptive reactogenicity (injection site and systemic) after each injection.	Phase II, randomized, observer-blind, multicentered study	CYD dengue vaccine (~5 log10 CCID50/ serotype 1, 2, 3, 4) Group 1: CYD dengue vaccine at D0, M6, and M12 Group 2: Placebo at D0, CYD dengue vaccine at M6 and M12 Group 3: Placebo at D0 and M6, CYD dengue vaccine at M12 CYD dengue vaccine either 1 year (Groups 1a, 2a, and 3a) or 2 years (Groups 1b, 2b, and 3b) after the primary series. 0.5 mL/injection. Subcutaneous injection.	Randomized: 1050 Group 1: 350 Group 2: 348 Group 3: 352	Colombia and the Philippines Endemic area 02 May 2016 to 20 Dec 2018 (interim CSR)	Healthy subjects 9–50 years	Ongoing Interim CSR (up to 28 days after booster injection at Year 1) Final CSR available in Q1 2021
CYD67	5.3.5.1	- NI of Gardasil humoral immune response after concomitant administration with CYD dengue vaccine compared to sequential administration, after last dose of Gardasil. - NI of the dengue humoral immune response after concomitant administration with Gardasil compared to sequential administration, after last dose of CYD dengue vaccine - Descriptive humoral immune response after each dose of Gardasil - Descriptive humoral immune response after each dose of CYD dengue vaccine - Descriptive safety of Gardasil and the CYD dengue vaccine after each and any injection in each group	Phase IIIb, randomized, open-label, multicenter study	CYD dengue vaccine (~5 log10 CCID50/ serotype 1, 2, 3, 4) Group 1: CYD dengue vaccine + Gardasil at D0 and M6, CYD dengue vaccine at M12 Group 2: Gardasil at D0 and M6; CYD dengue vaccine at M1, M7, and M13 0.5 mL/injection CYD dengue vaccine: subcutaneous injection Gardasil: intramuscular injection	Randomized: 528 Group 1: 266 Group 2: 262	Malaysia Endemic area 01 Dec 2016 to 27 May 2019	Healthy subjects 9–13 years	Completed Final CSR

Study Identifier	Location of Study Report	Main Objectives of the Study	Study design	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Countries; Endemic / Non-endemic Area; Trial Period (FVFS – LVLS*)	Healthy Subjects or Diagnosis of Patients	Study Status; Type of Report
CYD71	5.3.5.1	- NI of Cervarix humoral immune response after concomitant administration with CYD dengue vaccine compared to sequential administration, after last dose of Cervarix. - NI of the dengue humoral immune response after concomitant administration with Cervarix compared to sequential administration, after last dose of CYD dengue vaccine - Descriptive humoral immune response after each dose of Cervarix - Descriptive humoral immune response after each dose of CYD dengue vaccine - Descriptive safety of Cervarix and the CYD dengue vaccine after each and any injection in each group	Phase IIIb, randomized, open-label, multicenter study	CYD dengue vaccine (~5 log10 CCID50/ serotype 1, 2, 3, 4) Group 1: CYD dengue vaccine + Cervarix at D0 and M6, CYD dengue vaccine at M12 Group 2: Cervarix at D0 and M6; CYD dengue vaccine at M1, M7, and M13 0.5 mL/injection CYD dengue vaccine: subcutaneous injection Cervarix: intramuscular injection	Randomized: 480 Group 1: 239 Group 2: 241	Mexico Endemic area 16 Nov 2016 to 25 Mar 2019	Healthy subjects 9–14 years	Completed Final CSR

Table 22. Overview of individual pivotal and supportive studies for clinical immunogenicity and efficacy

Study Identifier	Location of Study Report	Main Objectives of the Study	Study design	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Countries; Endemic / Non-endemic Area; Trial Period (FVFS – LVLS*)	Healthy Subjects or Diagnosis of Patients	Study Status; Type of Report
CYD13	5.3.5.1	- Descriptive dengue humoral immune response before and after each injection. - Descriptive safety after each injection. - Detection of symptomatic dengue cases. - 6 months post-injection 3 safety follow-up.	Phase II, randomized, controlled, blind-observer (1st and 2nd injections), single blind (3rd injection), multicenter, multinational trial.	CYD dengue vaccine (~5 log10CCID50/ serotype 1, 2, 3, 4) Group 1: CYD dengue vaccine at D0, M6 and M12. Group 2: Placebo (NaCl 0.9%) at D0 and M6. Tdap† vaccine (ADACEL®) at M12. 0.5 mL/injection Placebo and CYD dengue vaccine: subcutaneous injection. Tdap vaccine: intramuscular injection.	Randomized: 600 - Group 1: 401 - Group 2: 199	Colombia Honduras Mexico Puerto Rico Endemic areas 09 Oct 2009 to 29 Aug 2011	Healthy subjects 9–16 years	Completed; Final CSR

Study Identifier	Location of Study Report	Main Objectives of the Study	Study design	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Countries; Endemic / Non-endemic Area; Trial Period (FVFS – LVLS*)	Healthy Subjects or Diagnosis of Patients	Study Status; Type of Report
CYD22	5.3.5.1	- Descriptive dengue humoral immune response before and after each injection. - Descriptive safety, after each injection. - 4-year post-injection 3 follow-up: antibody persistence and safety. - Detection of symptomatic dengue cases.	Phase II, randomized, controlled, blind-observer, monocenter trial.	CYD dengue vaccine (~5 log10CCID50 / serotype 1, 2, 3, 4) Group 1: CYD dengue vaccine at D0, M6 and M12. Group 2: Meningococcal Polysaccharide A+C vaccine at D0. Placebo (NaCl 0.4% containing human serum albumin 2.5%) at M6. Typhoid Vi Polysaccharide vaccine (Typhim Vi®) at M12. 0.5 mL/injection. Subcutaneous injection.	Randomized: 180 Group 1: 120 • 20 adults • 20 adolescents • 40 children (6–11 years) • 40 children (2–5 years) Group 2: 60 • 10 adults • 10 adolescents • 20 children (6–11 years) • 20 children (2–5 years)	Vietnam Endemic area 14 Mar 2009 to 12 Jul 2014 (including 4 years post-injection 3 follow-up)	Healthy subjects 2–45 years	Completed; Final CSR (up to 4 years post injection 3)
CYD24	5.3.5.1	- Descriptive dengue humoral immune response, before and after each injection, in children previously vaccinated against yellow fever. - Descriptive safety after each injection. - Vaccine viremia, after the first and second injections, in a subset of subjects. - Detection of symptomatic dengue cases. - 6-month post-injection 3 safety follow-up.	Phase II, randomized, controlled, blind-observer, monocenter trial.	CYD dengue vaccine (~5 log10CCID50/ serotype 1, 2, 3, 4) Group 1: CYD dengue vaccine at D0, M6 and M12. Group 2: Placebo (NaCl 0.4% containing human serum albumin 2.5%) at D0 and M6. Pneumococcal polysaccharide vaccine (Pneumo23®) at M12. 0.5 mL/injection. Subcutaneous injection.	Randomized: 300 (but 2 not vaccinated) Group 1: 199 • 99 children (6–11 years) • 100 children (2–5 years) Group 2: 99 • 49 children (6–11 years) • 50 children (2–5 years)	Peru Endemic area 26 Sep 2008 to 16 Aug 2010	Healthy subjects 2–11 years	Completed; Final CSR + Addendum to CSR with PRNT Data (retest)

Study Identifier	Location of Study Report	Main Objectives of the Study	Study design	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Countries; Endemic / Non-endemic Area; Trial Period (FVFS – LVLS*)	Healthy Subjects or Diagnosis of Patients	Study Status; Type of Report
CYD28	5.3.5.1	- Descriptive safety after each injection. - Descriptive dengue humoral response before and after each injection in a subset of subjects. - Descriptive cellular immune response after the 2nd and 3rd injection in a subset of subjects. - 4-year post-injection 3 follow-up: antibody persistence (in a subset of subjects) and safety. - Detection of symptomatic hospitalized dengue cases.	Phase II, randomized, controlled, blind-observer (1st injection), single blind (2nd and 3rd injection), multicenter trial.	CYD dengue vaccine (~5 log10CCID50/ serotype 1, 2, 3, 4) Group 1: CYD dengue vaccine at D0, M6 and M12. Group 2: If <12 years Placebo (NaCl 0.9%) at D0. Hepatitis A vaccine (Havrix®) at M6 and M12. If ≥ 12 years Placebo (NaCl 0.9%) at D0. Influenza vaccine (Vaxigrip®) at M6 and M12. 0.5 mL/injection. Subcutaneous injection for all but Hepatitis A vaccine: intramuscular injection.	Randomized: 1198 Group 1: 898 • 521 adults • 141 adolescents • 236 children Group 2: 300 • 174 adults • 46 adolescents • 80 children	Singapore Endemic area 07 Apr 2009 to 29 Oct 2014; (including 4 years post-injection 3 follow-up)	Healthy subjects 2–45 years	Completed; Final CSR
CYD30	5.3.5.1	- Descriptive dengue humoral immune response before and after each injection. - Descriptive safety after each injection. - Detection of symptomatic dengue cases. - 6-month post-injection 3 safety follow-up.	Phase II, randomized, placebo-controlled, blind-observer, monocenter trial.	CYD dengue vaccine (~5 log10CCID50/ serotype 1, 2, 3, 4) Group 1: CYD dengue vaccine at D0, M6 and M12. Group 2: Placebo (NaCl 0.9%) at D0, M6 and M12. 0.5 mL/injection. Subcutaneous injection.	Randomized: 150 Group 1: 100 • 60 adolescents (12 to 16 years) • 40 children (9 to 11 years) Group 2: 50 • 31 adolescents (12 to 16 years) • 19 children (9 to 11 years)	Brazil Endemic area 20 Aug 2010 to 15 May 2012	Healthy subjects 9–16 years	Completed; Final CSR.

Study Identifier	Location of Study Report	Main Objectives of the Study	Study design	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Countries; Endemic / Non-endemic Area; Trial Period (FVFS – LVLS*)	Healthy Subjects or Diagnosis of Patients	Study Status; Type of Report
CYD23	5.3.5.1	- Vaccine efficacy against virologically-confirmed symptomatic dengue cases post-Dose 3 - Descriptive dengue humoral immune response, before and after each injection and one year after the 3rd injection, in a subset of subjects. - Safety throughout the trial and descriptive reactogenicity (injection site and systemic), after each injection, in a subset of subjects. - Vaccine viremia, after the 1st and 2nd injections, in a subset of subjects.	Phase IIb, randomized, controlled, blind-observer, monocenter trial.	CYD dengue vaccine (~5 log10CCID50/ serotype 1, 2, 3, 4) Group 1: CYD dengue vaccine - cohort 1: at D0, M6 and M12. - cohort 2: at D0, M6 and M12. Group 2: - cohort 1: Rabies vaccine (Verorab®) at D0. Placebo (NaCl 0.9%) at M6 and M12. - cohort 2: Placebo at D0, M6 and M12. 0.5 mL/ injection. Subcutaneous injection.	Randomized: 4002 Two-step enrollment as per cohort number : Group 1: 2669 • 100 in cohort 1 • 2569 in cohort 2 Group 2:1333 • 50 in cohort 1 • 1283 in cohort 2	Thailand Endemic area 05 Feb 2009 to 22 Mar 2012 (13 months after injection 3: end of Active Phase) End of the study (after a hold): 10 Sep 2013	Healthy subjects 4–11 years	Completed; Final CSR
CYD32	5.3.5.1	- Descriptive safety, after each injection. - Descriptive dengue humoral immune response, after the 2nd and 3rd injection. - 6-month post-injection 3 safety follow-up.	Phase III, randomized, placebo-controlled, blind-observer, multicenter trial.	CYD dengue vaccine (~5 log10CCID50/ serotypes 1, 2, 3, 4) Group 1: CYD dengue vaccine at D0, M6 and M12. Group 2: Placebo (NaCl 0.9%) at D0, M6 and M12. 0.5 mL/ injection. Subcutaneous injection.	Randomized: 250 Group 1: 199 • 99 (2–5 years) • 100 (6–11 years) Group 2: 51 • 26 (2–5 years) • 25 (6–11 years)	Malaysia Endemic area 02 Dec 2010 to 14 Aug 2012	Healthy subjects 2–11 years	Completed; Final CSR

* FVFS – LVLS: First visit of the first subject – last visit of the last subject (LVLS includes last contact of subjects by telephone call)
† Tetanus toxoid, reduced Diphtheria toxoid and acellular Pertussis vaccine, absorbed

The CHMP acknowledged that, at the time of the initial MAA, the integrated immunogenicity analysis comprised data from 16 clinical studies that assessed immunogenicity of the final formulation of the CYD dengue vaccine administered as a three-dose schedule 6 months apart. The 16 clinical studies comprised 2 large-scale pivotal efficacy studies CYD14 and CYD15 and 14 supportive studies, i.e. 9 Phase II (CYD08, CYD12, CYD13, CYD22, CYD24, CYD28, CYD30, CYD47 and CYD51), 1 Phase IIb (CYD23) and 4 Phase III (CYD17, CYD29, CYD32 and CYD33).

Studies CYD12, CYD17, CYD47, CYD51 included 18-45 yoa adults only and are therefore not included in the present integrated immunogenicity analysis. All 3 CYD08, CYD29, CYD33 studies were also discarded from the present analysis since they included infants who were of 9-15 months of age at first injection.

In addition to the above-mentioned studies, results of the following studies were included in the present analysis: CYD65, CYD67, CYD71. These studies were completed (CYD67, CYD71) or achieved a milestone (CYD65, which is still ongoing) after the approval of Dengvaxia. Studies CYD14 and CYD15 include a 5-year FU and are now completed.

Three additional studies were completed since the initial MA, namely CYD63, CYD64 and CYD66. CYD63 and CYD64 assessed the effect of a booster dose of the CYD dengue vaccine 4 to 5 years after the third dose (PD3) of the primary series administered in previous studies (CYD28 and CYD13/30, respectively). CYD66 investigated the effect of dTpa co-administration. All 3 studies included adults only and are therefore not included in this submission.

Consequently, it is considered by the CHMP that data from all relevant studies were included in the integrated immunogenicity analysis. This leads to a total of 12 studies used for this extension of indication application.

Integrated analysis compared immunogenicity results obtained in children and adolescents from 2-5 years, 6-8 years and 9-17 years of age. These age ranges were based on the observed results submitted at initial MAA. The fact that children <9 yoa, and particularly children 6-8 yoa, may benefit from vaccination was discussed during the initial MAA.

2.4.2. Immunogenicity methods

This section summarizes the methodology used in the 12 individual studies relevant to the immunogenicity assessments. Please refer to the efficacy section for Methodology specifically related to efficacy assessments.

2.4.2.1. Overall design

Studies were conducted in healthy subjects (age ranging from 2 to 50 years) in dengue endemic regions, where the disease has been continuously present in the native population with documented outbreaks or epidemics. Two dengue endemic regions are represented: Asia Pacific (AP) (studies CYD22, CYD28, CYD32, CYD23, CYD14, CYD67, and CYD65) and Latin America and the Caribbean (LatAm) (studies CYD13, CYD24, CYD30, CYD15, CYD71 and CYD65). Subjects had to fulfil all inclusion and exclusion criteria prior to enrolment.

The subjects involved in all studies were randomized for treatment assignment using an interactive voice response system (IVRS). Randomization using the permuted block method guarantees the independence of treatment assignment and outcome. The randomization of subjects was stratified by center for studies that were multi-center. In addition, 7 studies (CYD22, CYD24, CYD28, CYD32, CYD14, CYD15, and CYD65) were also stratified by age.

Table 23. Age ranges used for stratification across studies stratified by age

Study Code	CYD22	CYD24	CYD28	CYD32	CYD14	CYD15	CYD65
Age of enrolled subjects	2-45 years	2-11 years	2-45 years	2-11 years	2-14 years	9-16 years	9-50 years
Age for Stratification							
Children							
2-5	x	x		x	x		
2-11			x				
6-11	x	x		x	x		
9-11						x	x
Adolescents							
12-14					x		
12-16						x	
12-17	x		x				x
Adults							
18-39							x
18-45	x		x				
40-50							x

Source: Modified from each individual CSRs

All studies were blind-observer and controlled with at least one injection of placebo, i.e. a sodium chloride solution or an active control selected to provide a benefit to the study population. The laboratory was blinded to the treatment group when performing all testing.

Duration of subject participation varied across studies. For CYD13, CYD24, CYD30, and CYD32, subjects were followed up for safety up to 6 months after the last study vaccine injection. For CYD23, subjects were followed-up for efficacy and safety (all subjects) as well as immunogenicity (randomized subset of subjects) up to 1 year after the last study vaccine injection. CYD23 subjects continued the safety surveillance through CYD57, a 4-year follow-up study. For CYD22 and CYD28, subjects were followed-up for safety (all subjects) and immunogenicity (randomized subset of subjects) up to 4 years after the last study vaccine injection. For CYD14 and CYD15, subjects were followed-up for efficacy (all subjects),

safety (all subjects) and immunogenicity (randomized subset of subjects) up to 5 years after the last study vaccine injection. Concomitant administration studies CYD67 and CYD71 included the follow-up for safety up to 6 months after the last study vaccine injection. For CYD65, subjects were to be followed-up for immunogenicity (all subjects in Stage I, and seropositive subjects in Stage II) up to 28 days post-booster injection and for safety (all subjects) up to 6 months post-booster injection. Booster administration was to take place either 1 year or 2 years after the last vaccine injection from primary series.

The CHMP considered that all 12 clinical trials were conducted in healthy subjects (2-50 yoa) in endemic regions (Asia Pacific and Latin America and the Caribbean) and are consistent in terms of the general study design, vaccine formulation and schedule. The age range of the randomised population varied widely across studies. Only one study enrolled seropositive subjects only (CYD65). All other studies enrolled subjects irrespective of serostatus. All the studies assessed immunogenicity and safety, CYD23 was a POC efficacy trial, CYD24 assessed CYD dengue vaccine in children previously vaccinated YF, CYD22 and CYD28 assessed immune persistence at 4 years, CYD65 was a booster study, and CYD67 and CYD71 were coadministration studies (tetravalent and bivalent HPV vaccines).

The design of most of the individual studies was already assessed at initial MAA and deemed appropriate. The laboratory was blinded to the treatment group when performing all testing. The FU duration varied across studies. Pre-dose 1 (PreD1) and Post-dose 3 (PD3) data were used for performing the integrated immunogenicity analysis. Data obtained after a longer duration following post-last injection were analysed to assess Ab persistence.

2.4.2.2. Immunogenicity assessment

Dengue immunogenicity

In all individual pivotal and supportive studies, the neutralizing Ab response was measured using PRNT, which is considered as the "gold standard" assay method. The PRNT assay allows quantitation of neutralizing Ab for each serotype and the neutralizing titer is expressed as the highest reciprocal dilution of sera that reduced the infectivity of a challenge virus by 50% (PRNT50 most commonly used). The PRNT assay as developed by Sanofi Pasteur evolved during the course of the development and was optimized and validated. Seropositivity was defined as a neutralizing Ab level ≥ 10 1/dil against at least one dengue serotype. This level of Ab is accepted as predictive of protection for JE and is used here for the purposes of seropositivity analysis. There are currently no serological correlates of protection accepted for dengue.

PRNT50 has been used during the clinical development to assess the humoral immune response after dengue vaccination.

Definition of Baseline Dengue

Baseline information about previous dengue infection was based on self-reporting and collected using various questionnaires across studies. However, as infection might have been asymptomatic or a subject might not recall accurately a previous infection, dengue serostatus was assessed based on the detection of neutralizing Abs in blood samples collected at enrolment using a PRNT50 assay.

Dengue immune status at baseline is defined as:
(i) Seropositive: subjects with quantified (≥ 10 [1/dil], the lower limit of quantitation [LLOQ]) neutralizing Ab against at least 1 dengue serotype in the baseline sample.
(ii) Seronegative: subjects without quantified (< LLOQ) neutralizing Abs against all of the 4 dengue serotypes in the baseline sample.
(iii) Undetermined: subjects with no titer ≥ LLOQ and at least one missing titer.

Collection of Data

In all studies, blood samples intended for dengue PRNT50 testing were collected at baseline and after the third injection of the CYD dengue vaccine. Blood samples were also collected at different timepoints depending on the study design and intent.

In study CYD28 and in the 3 efficacy studies CYD14, CYD15, and CYD23/57, blood samples were collected prior to vaccination in a subset of subjects and used to determine the baseline serological status. The 'Immunogenicity Subset' consisted of 2000 randomly selected subjects in each CYD14 and CYD15 and 300 non-randomly selected subjects in CYD23 (i.e. first subjects enrolled in the study) to provide the baseline blood samples and additional samples to assess immunogenicity.

Table 24. Post-injection blood sample collection for dengue PRNT50 testing in individual studies

Post-injection timepoints	Studies 28 days after injection	Studies 30 days after injection
PD1, PD2 and PD3‡	CYD13, CYD22, CYD24, CYD67, CYD71	CYD23, CYD30
PD2 and PD3	CYD14*, CYD15*, CYD28, CYD32, CYD65 (Group 1)	-
PD1 and PD2	CYD65 (Group 2)	-
Yearly (long-term follow-up studies) †	CYD14*, CYD15*, CYD22, CYD28, CYD65	-

* In CYD14 and CYD15, immunogenicity at these time points was assessed only in a subset of subjects (see below)

† For long-term studies, the immunogenicity evaluation was also performed each year: up to 4 years (CYD22 and CYD28) and up to 5 years (CYD14 and CYD15) after the last injection. In CYD65, immunogenicity was also to be assessed 1 year (all subjects) and 2 years (subjects receiving the Year 2 booster injection) after the last injection.

‡ PD : post-dose

Source: Modified from each individual CSR

The CHMP noted that dengue immunogenicity was evaluated based on PRNT50 results. The validated PRNT50 assay was the core immunologic assay for measuring functional antibodies able to neutralize dengue virus in studies submitted at the initial MAA. No immune correlate of protection is currently established for dengue but based on current knowledge it was considered adequate that immunogenicity assessment for CYD vaccine was based on neutralising antibody titres. The assay methodology is in line with WHO recommendation and was considered acceptable.

Serological cross-reactivity amongst members of the Flaviviridae family (DENV, Yellow Fever (YF), West-Nile virus (WNV), Japanese Encephalitis virus (JEV) and Tick borne encephalitis virus (TBEV)) is a well-known diagnostic problem. Hence misclassification of subjects (false positives) cannot be excluded.

Analysis by using dengue PRNT with a higher stringency (PRNT90) were not performed or not presented in the context of this application. Such assay was used during the initial evaluation to reanalyse blood samples for post-hoc efficacy analyses by dengue immune status at baseline. Using a more stringent assay may likely lead to lower false positive rate resulting from flaviviruses cross-reactivity, but it would also run the risk of a higher false negative rate, resulting in, most probably, even lower number of seropositive subjects to be included in the analysis.

Altogether, it is considered that the use of PRNT50 to determine dengue immunogenicity in the present integrated analysis is acceptable.

The dengue serostatus at baseline was defined as previously, i.e. seropositive if the PRNT50 titre was ≥10 against at least one serotype and seronegative if PRNT50 titre was < LLOQ against any of the four dengue serotypes in the baseline sample. This threshold represents the lower limit of quantification (LLOQ).

In all studies, blood samples intended for dengue PRNT50 testing were collected at baseline, either in all subjects or in a subset, and after the third injection of the CYD dengue vaccine.

2.4.2.3. Methods of analysis for immunogenicity

General biostatistical methods of analysis used in the individual studies and in the updated integrated immunogenicity analysis are summarized hereunder.

Definition of the Study Populations

The statistical populations used in the individual studies are considered clinically similar and are fully described in each individual CSR. The definitions of the study populations used in the integrated immunogenicity analysis were the same as those used in the individual studies. Subjects were analyzed by the treatment group to which they were randomized.

All individual studies presented both a per-protocol analysis set (PPAS) that included all subjects who meet the per protocol criteria as defined in each individual study and a full analysis set (FAS) defined as all subjects who received at least one injection of the CYD dengue vaccine or control vaccine, and who had at least 1 blood sample drawn and 1 valid post-injection serology result. In studies in which only a subset of subjects was followed-up for immunogenicity (i.e. CYD14, CYD15, CYD23, CYD28), the FAS for the Immunogenicity Subset (FASI) was defined as described for the FAS. According to the MAH, Similar results between the FAS and the PPAS were observed in all individual studies. Therefore, only the FAS (and/or the FASI, as appropriate) were used in the integrated immunogenicity analysis.

The integrated immunogenicity analysis presented is performed on an updated clinical database (prior database updated with most recent clinical data). Data presented correspond to seropositive subjects from the FAS and/or FASI from the following studies: CYD13, CYD14, CYD15, CYD22, CYD24, CYD28, CYD30, CYD23/57, CYD32, CYD65 (intermediate results), CYD67, and CYD71.

It is to note that data included in the updated integrated analysis from the following studies were restricted as indicated: (i) CYD67 and CYD71 data were restricted to the sequential interventional treatment (one study arm), (ii) CYD65 data were restricted to the Group 1 receiving 3 doses.

Calculation of Confidence Intervals

The methods for computing the confidence intervals (CIs) were as follows:

• CI for point estimate of percentages of seropositivity: the 95% CIs for percentages were calculated using the exact binomial Clopper-Pearson's method, quoted by Newcombe.

• CI for point estimate of GMTs and GMTRs: assuming that log10 transformation of the titers / data follows a normal distribution, at first, the mean and the 95% CI were calculated on log10 (titers / data) using the usual calculation for normal distribution (using Student's t distribution with n-1 degree of freedom). Antilog transformations were then applied to the results of calculations, in order to provide geometric means (GMT or GMTR) and their 95% CI.

Statistical Criteria for Assessment

Overall, assessment of the immune response for each serotype was consistent across studies. Thus, GMTs for each serotype was assessed at baseline and either 28 days or 30 days after injection, and at

additional timepoints in studies with a Long-Term Follow-Up (LTFU). The GMTRs were also assessed to provide additional information in studies conducted in endemic regions where subjects might have detectable Ab levels before first injection due to natural infection, to reflect the increase in the immune response after vaccine injection for each serotype as compared to baseline, or depending on the study design, to the immune response after a given injection.

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

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

The assessment criteria used in the integrated immunogenicity analysis were the same as those used in the individual studies (i.e. GMTs and GMTRs). GMTs were assessed after each injection (when available), and GMTRs against each serotype using PD1, PD2 or PD3 titers over baseline titers (when available).

For an overview of the CYD dengue vaccine immune response persistence (long term studies), GMTs against each serotype per age group, study, and region were assessed yearly after the last vaccine injection (primary series), and GMTRs assessed yearly using yearly titers over either baseline titers or titers after the last vaccine injection (as available).

Additionally, graphical presentations by reverse cumulative distribution curves (RCDC) by serotype are presented after a given vaccine dose in baseline dengue seropositive subjects from the CYD dengue vaccine Group, according to age group and region, and up to 5 years after the third injection.

Statistical Methodology

In all individual studies, the immunogenicity analyses were descriptive and no hypothesis was tested. Statistical methodologies for each individual study are detailed in each individual CSR. The statistical methods for the integrated immunogenicity analysis are summarized below and are further detailed in the Integrated Immunogenicity Analysis Report.

The analyses were descriptive and included various endpoints and parameters that are consistent with those presented in the individual studies.

Based on the immunogenicity trends observed in the Phase I and Phase II studies, the Integrated Immunogenicity Analysis was presented according to region and age: (i) Region: endemic AP and endemic LatAm, (ii) Age: subjects 6 to 8 years, along with subjects aged 2 to 5 and 9 to 17 years as benchmark.

The baseline characteristics taken into consideration were gender, age, and ethnic origin.

The data presented in the Integrated Immunogenicity Analysis were not pooled and are presented by study, because, in endemic regions (Asia Pacific and Latin America), the dengue antibody responses may be correlated with the baseline antibody levels. Therefore, the results are expected to be study- and population-related, and thus by nature not adapted for study pooling. Additionally, previous exposure to either YF or JE vaccine or natural infection may have an effect on the vaccine response (ISI body document, 1.8.1.2).

Handling of Missing Data

Missing data were not estimated. No search for outliers was performed (immunogenicity data were considered validated).

The following rules were followed to consider Ab titers < LLOQ:
• For computation of GMTs, any titer reported as < LLOQ was converted to a value of ½LLOQ;
• For calculation of GMTRs, < LLOQ was converted to ½LLOQ for a numerator and < LLOQ was converted to LLOQ for a denominator.
There was no upper limit of quantitation (ULOQ) with the dengue PRNT method.

The CHMP acknowledged that analyses were performed on the full analysis set (FAS) or the FAS for the immunogenicity subset (FASI), as appropriate. The FAS was defined as all subjects who received at least one injection of the CYD dengue vaccine or control vaccine, and who had at least 1 blood sample drawn and 1 valid post-injection serology result. In studies in which only a subset of subjects was followed-up for immunogenicity (i.e. CYD14, CYD15, CYD23, CYD28), the FASI was defined as described for the FAS.

Results of all relevant studies (n=12) were included in the integrated immunogenicity analysis.

The main objective of the integrated immunogenicity analysis was to provide an overview of the humoral immune response against each and any dengue serotype induced by the CYD dengue vaccine, according to age and region, in baseline dengue seropositive subjects, with a focus on the response 28 days PD3. The presentation of analysis by the selected age groups is appropriate. The Ab titers against any serotype induced by CYD dengue vaccine were not found. This issue is not pursued since analysis by serotype is considered the most relevant.

Analyses were not pooled between both endemic regions (AP and LatAm) which is deemed appropriate because of difference in epidemiology, in age range, and in YF/JE vaccination status. Results could be expected to be study- and population-related. Results were presented by study to give an overview of the GMTs range, but were also presented pooled for the Endemic AP region.

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

GMTs were assessed after each injection (when available), and GMTRs against each serotype using PD3 titers over baseline titers (when available).

Finally, rules for converting Ab titers reported as < LLOQ are deemed appropriate for both GMTs and GMTRs calculation.

2.4.3. Immunogenicty results

2.4.3.1. Comparison and analyses of results across studies

This section presents the results obtained through the updated integrated immunogenicity analysis performed on seropositive subjects, presented by region and age group.

Study Populations

For studies CYD13, CYD22, CYD24, CYD30, CYD32, CYD67, CYD71, and CYD65, the disposition of subjects is based on the FAS, and for CYD14, CYD15, CYD23 and CYD28, the disposition of subjects is based on the FASI.

In studies conducted in endemic regions, the proportion of baseline dengue seropositive subjects increased with age and, among subjects with an available baseline serostatus, were for the CYD dengue vaccine group and control group, respectively:

- 49.2% (373/758) and 47.5% (163/343) for 2 to 5 years;
- 55.4% (292/527) and 62.0% (152/245) for 6 to 8 years;
- 70.3% (2544/3620) and 74.4% (1005/1350) for 9 to 17 years.

The demographic characteristics of subjects contributing to the immunogenicity results presented in the tables below. In each study, the male/female ratio within each study group was relatively well balanced, considering the limited number of subjects included per study group. Mean age of subjects among the different age groups was very similar between the CYD dengue vaccine and the control groups. Ethnicity was collected in all studies, except for CYD22, CYD23, CYD24, CYD28, CYD67, and CYD71. In AP endemic regions, almost 90% of subjects were of Asian origin (both study groups). In LatAm endemic regions, most subjects were of Hispanic origin, of mixed ethnic origin in CYD15 and reported as "other" (both study groups).

Table 25. Demographics at baseline - seropositive subjects aged 9-17 years - FAS and FASI

		CYD Dengue Vaccine			Control		
Region	**Study**	**N**	**Male n (%)**	**Mean Age (yrs)**	**N**	**Male n (%)**	**Mean Age (yrs)**
Endemic AP	**CYD14**	485	244 (50.3)	11.8	**251**	**122 (48.6)**	**11.8**
	CYD22	25	13 (52.0)	11.2	**15**	**8 (53.3)**	**11.5**
	CYD23	58	27 (46.6)	9.66	**21**	**8 (38.1)**	**9.67**
	CYD28	31	19 (61.3)	12.8	**13**	**8 (61.5)**	**12.5**
	CYD32	22	13 (59.1)	10.1	**9**	**6 (66.7)**	**10.0**
	CYD65	139	71 (51.1)	12.4	-	-	-
	CYD67*	88	29 (33.0)	10.6	-	-	-
	All	848	416 (49.1)	11.6	**309**	**152 (49.2)**	**11.6**
Endemic LatAm	**CYD13**	301	151 (50.2)	12.2	155	70 (45.2)	12.2
	CYD15	1048	496 (47.3)	11.9	495	264 (53.3)	12.0
	CYD24	24	8 (33.3)	10.1	11	6 (54.5)	9.82
	CYD30	68	31 (45.6)	12.9	35	23 (65.7)	12.4
	CYD65	104	58 (55.8)	12.7	-	-	-
	CYD71†	151	-	9.68	-	-	-
	All	1696	744 (43.9)	11.8	696	363 (52.2)	12.0

n: number of subjects fulfilling the item listed
* By study design, enrolled subjects were females: males at a ratio 2:1 (HPV/CYD - concomitant administration study)
† By study design, enrolled subjects were females (HPV/CYD - concomitant administration study)

Source: Modified from 5.3.5.3 Integrated Immunogenicity Analysis Report, Table 3.9.3.3 (see "Integrated Summary of Immunogenicity [ISI] - Tables and Figures" submitted in eCTD sequence 0029)

Table 26. Demographics at baseline - seropositive subjects aged 6-8 years - FAS and FASI

		CYD dengue vaccine Group			Control Group		
Region	Study	N	Male n (%)	Mean Age (yrs)	N	Male n (%)	Mean Age (yrs)
Endemic AP	CYD14	168	81 (48.2)	6.93	88	46 (52.3)	6.90
	CYD22	17	10 (58.8)	7.18	4	2 (50.0)	7.00
	CYD23	66	27 (40.9)	7.15	38	17 (44.7)	7.26
	CYD28	8	4 (50.0)	7.25	3	2 (66.7)	7.00
	CYD32	22	8 (36.4)	7.09	3	3 (100.0)	7.33
	All	281	130 (46.3)	7.02	136	70 (51.5)	7.01
Endemic LatAm	CYD24	11	7 (63.6)	6.64	16	4 (25.0)	7.00
	All	11	7 (63.6)	6.64	16	4 (25.0)	7.00

n: number of subjects fulfilling the item listed

Source: Modified from 5.3.5.3 Integrated Immunogenicity Analysis report, Table 3.9.6.3

Table 27. Demographics at baseline - seropositive subjects aged 2-5 years - FAS and FASI

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

n: number of subjects fulfilling the item listed

Source: Modified from 5.3.5.3 Integrated Immunogenicity Analysis report, Table 3.1.1.3

The CHMP noted that twelve studies were included in the integrated immunogenicity analysis but only results of 6 of them were used to compare Pre-D1 and PD3 data by age, since CYD65, CYD67, CYD13, CYD15, CYD30 and CYD71 did not include children from 2-8 yoa.

Children 6-8 years are nearly exclusively from AP countries (as are children from 2-5 years), while children 9-17 are from both regions, although mainly from LatAm.

All studies were conducted in endemic regions. The proportion of baseline dengue seropositive subjects increased with age, which is consistent with the dengue epidemiology and the observation made during the initial MAA. Seropositivity rates at baseline were overall well balanced between vaccine and control groups and were, respectively, 47.5%-49.2% for 2 to 5 years, 55.4%-62.0% for 6 to 8 years, and 70.3%-74.4% for 9 to 17 years.

Several studies included only very few seropositive subjects, particularly in the 2-5 and 6-8 years age groups, either in the vaccine or control groups or in both groups. In contrast to the 9-17 years age group, less subjects from 2-8 yoa were included in studies conducted in LatAm when compared to AP regions. Only one LatAm study (CYD24) included both adolescents of 9-17 yoa and children of 2-8 yoa.

In the 9-17 yoa age group, a total of 848 and 309 subjects were included in, respectively, the vaccine and control groups of studies conducted in AP region whereas, in studies conducted in the LatAm region, a total of 1696 and 696 subjects were included in, respectively, the vaccine and control groups. Of these 1696 vaccinees, only 24 were included in the CYD24 study.

In the 6-8 yoa age group, a total of 281 and 136 subjects were included in, respectively, the vaccine and control groups of studies conducted in AP region whereas, in studies conducted in the LatAm region, a total of 11 and 16 subjects were included in, respectively, the vaccine and control groups.

In the 2-5 yoa age group, a total of 334 and 142 subjects were included in, respectively, the vaccine and control groups of studies conducted in AP region whereas, in LatAm region, a total of 39 and 21 subjects were included in the vaccine and control groups respectively.

Consequently, some imbalance in gender were observed between vaccine and placebo groups in certain studies. Mean age were generally well balanced between both groups in each of the studies. Another consequence of this limited number of included subjects in some studies is difficult result interpretation (see below).

Comparison of Results to Support the Indication in Baseline Dengue Seropositive Subjects aged 6 to 8 Years (3-Dose Schedule)

GMTs at baseline and 28 days after the third injection of the CYD dengue vaccine are presented in baseline seropositive subjects aged 9 to 17, 6 to 8, and 2 to 5 years by endemic region in the tables below.

Pre-Dose 1 GMTs were higher in older subjects than in younger subjects (i.e. GMTs in 9 to 17 years > 6 to 8 years > 2 to 5 years) and higher in high endemic settings compared to low endemic settings, as anticipated, due to higher natural dengue exposure.

Overall, a trend towards higher PD3 GMT levels was observed in subjects with higher baseline titers in all age groups. As a consequence, a trend towards increasing PD3 GMTs with increasing age and higher endemicity was also observed. Therefore, lowest GMTs were generally observed in subjects aged 2 to 5 years or in studies conducted in countries with lower dengue endemicity such as Singapore (CYD28), where baseline GMTs were lower.

In seropositive subjects aged 6 to 8 years, an increase in GMTs was observed for each of the 4 serotypes after 3 doses of the CYD dengue vaccine across the reported trials, with higher values for serotypes 1, 2, and 3 and lower levels for serotype 4, overall as a consequence of lower pre-Dose 1 levels for serotype 4.

Neutralizing Ab levels in the control group, overall, showed no increase in GMTs after any injection of the placebo, across the reported trials, in all age groups.

Table 28. Geometric means of Dengue PRNT50 antibody (1/dil) pre-Dose 1 and PD3 for each serotype, in seropositive subjects aged 9 to 17 years

				CYD Dengue vaccine											
				Serotype 1			Serotype 2			Serotype 3			Serotype 4		
Age group Region	Region	Study	N	Pre-dose 1 GM (M) (95% CI)	Post-dose 3 GM (M) (95% CI)	N	Pre-dose 1 GM (M) (95% CI)	Post-dose 3 GM (M) (95% CI)	N	Pre-dose 1 GM (M) (95% CI)	Post-dose 3 GM (M) (95% CI)	N	Pre-dose 1 GM (M) (95% CI)	Post-dose 3 GM (M) (95% CI)
9-17 years	Endemic AP	CYD14	485	167 (481)	437 (482)	485	319 (482)	793 (481)	485	160 (477)	443 (481)	485	83.8 (483)	272 (481)
				(138; 202)	(373; 511)		(274; 373)	(704; 892)		(135; 190)	(387; 507)		(72.0; 97.6)	(245; 302)
		CYD22	25	116 (25)	328 (24)	25	177 (25)	654 (24)	25	68.8 (25)	234 (24)	25	39.8 (25)	254 (24)
				(44.6; 303)	(152; 706)		(90.2; 348)	(349; 1226)		(37.9; 125)	(141; 389)		(21.3; 74.6)	(147; 440)
		CYD23	58	214 (58)	461 (56)	58	281 (58)	645 (56)	58	117 (58)	532 (56)	58	81.2 (58)	231 (56)
				(118; 386)	(259; 819)		(164; 479)	(424; 981)		(71.5; 191)	(350; 810)		(51.0; 129)	(183; 293)
		CYD28	31	20.4 (31)	153 (28)	31	48.0 (31)	268 (28)	31	30.6 (31)	294 (28)	31	13.1 (31)	209 (28)
				(8.81; 47.2)	(69.1; 339)		(19.4; 119)	(134; 536)		(17.5; 53.6)	(175; 495)		(7.76; 22.1)	(155; 282)
		CYD32	22	163 (22)	418 (22)	22	247 (22)	661 (22)	22	162 (22)	597 (22)	22	57.6 (22)	315 (22)
				(59.4; 449)	(163; 1071)		(88.1; 690)	(258; 1692)		(76.7; 343)	(266; 1343)		(25.9; 128)	(166; 598)
		CYD65*	44	76.9 (44)	637 (43)	44	125 (44)	678 (43)	44	258 (44)	770 (43)	44	64.2 (44)	434 (43)
				(43.5; 136)	(404; 1003)		(83.7; 187)	(486; 947)		(156; 426)	(507; 1171)		(42.3; 97.3)	(319; 590)
		CYD67	88	82.4 (88)	453 (84)	88	133 (88)	717 (84)	88	97.8 (87)	549 (84)	88	25.2 (88)	303 (84)
				(50.0; 136)	(313; 656)		(86.4; 204)	(526; 977)		(65.7; 146)	(411; 734)		(17.1; 37.2)	(255; 359)
	Endemic LatAm	CYD13	301	182 (301)	680 (272)	301	244 (301)	832 (272)	301	218 (301)	926 (272)	301	72.4 (301)	371 (272)
				(144; 229)	(558; 829)		(199; 300)	(712; 972)		(178; 267)	(791; 1084)		(60.2; 87.1)	(327; 422)
		CYD15	1048	278 (1046)	703 (1040)	1048	306 (1048)	860 (1040)	1048	261 (1048)	762 (1040)	1048	73.3 (1046)	306 (1040)
				(247; 313)	(634; 781)		(277; 338)	(796; 930)		(235; 289)	(699; 830)		(66.6; 80.7)	(286; 328)

				CYD Dengue vaccine											
				Serotype 1			Serotype 2			Serotype 3			Serotype 4		
Age group Region	Region	Study	N	Pre-dose 1 GM (M) (95% CI)	Post-dose 3 GM (M) (95% CI)	N	Pre-dose 1 GM (M) (95% CI)	Post-dose 3 GM (M) (95% CI)	N	Pre-dose 1 GM (M) (95% CI)	Post-dose 3 GM (M) (95% CI)	N	Pre-dose 1 GM (M) (95% CI)	Post-dose 3 GM (M) (95% CI)
		CYD24	24	203 (24)	392 (23)	24	218 (24)	389 (23)	24	147 (24)	285 (23)	24	27.1 (24)	207 (22)
				(81.6; 504)	(186; 826)		(90.3; 524)	(196; 772)		(86.2; 251)	(164; 497)		(13.2; 55.4)	(136; 315)
		CYD30	68	109 (68)	567 (63)	68	219 (68)	1246 (63)	68	293 (68)	1470 (63)	68	24.8 (68)	513 (63)
				(71.4; 165)	(393; 816)		(156; 306)	(917; 1694)		(178; 481)	(1016; 2128)		(18.2; 33.7)	(386; 683)
		CYD65	31	75.2 (31)	280 (30)	31	166 (31)	584 (30)	31	151 (31)	393 (30)	31	64.7 (31)	376 (30)
				(35.6; 159)	(165; 473)		(83.7; 331)	(356; 958)		(67.7; 339)	(228; 677)		(29.0; 144)	(230; 612)
		CYD71	151	108 (151)	393 (140)	151	188 (151)	735 (140)	151	90.2 (151)	388 (140)	151	38.0 (151)	265 (140)
				(72.1; 163)	(292; 528)		(135; 262)	(575; 940)		(67.2; 121)	(325; 463)		(28.4; 50.9)	(220; 320)

M: number of subjects with available Ab titer for the relevant endpoint

*For CYD65 only Group 1 is included (CYD65 Stage I (primary series) subjects received either 3 injections of CYD dengue vaccine or placebo 6-months apart; ie, CYD/CYD/CYD [Group1], PLA/CYD/CYD [Group 2], and PLA/PLA/CYD [Group3])

Source: Modified from 5.3.5.3 Integrated Immunogenicity Analysis report, Table 3.9.3.7

Table 29. Geometric means of Dengue PRNT50 antibody (1/dil) pre-Dose 1 and PD3 for each serotype, in seropositive subjects aged 6 to 8 years

				Serotype 1			Serotype 2			Serotype 3			Serotype 4	
Region	Study	N	Pre-dose 1 GM (M) (95% CI)	Post-dose 3 GM (M) (95% CI)	N	Pre-dose 1 GM (M) (95% CI)	Post-dose 3 GM (M) (95% CI)	N	Pre-dose 1 GM (M) (95% CI)	Post-dose 3 GM (M) (95% CI)	N	Pre-dose 1 GM (M) (95% CI)	Post-dose 3 GM (M) (95% CI)
Endemic AP	CYD14	168	80.8 (167)	203 (166)	168	118 (168)	369 (166)	168	105 (168)	316 (166)	168	48.4 (168)	175 (166)
			(57.3; 114)	(154; 268)		(86.0; 161)	(298; 457)		(75.5; 145)	(244; 411)		(37.2; 63.0)	(145; 211)
	CYD22	17	47.3 (17)	133 (15)	17	41.8 (17)	147 (15)	17	44.2 (17)	135 (15)	17	16.0 (17)	134 (15)
			(13.6; 164)	(51.3; 343)		(16.2; 108)	(74.0; 292)		(20.5; 95.3)	(76.8; 237)		(8.32; 30.9)	(95.0; 190)
	CYD23	66	66.5 (66)	213 (63)	66	118 (66)	548 (63)	66	49.5 (66)	462 (63)	66	53.8 (66)	195 (63)
			(39.4; 112)	(138; 329)		(69.0; 202)	(355; 844)		(34.8; 70.5)	(328; 651)		(35.2; 82.2)	(141; 269)
	CYD28	8	6.75 (8)	101 (8)	8	8.97 (8)	89.0 (8)	8	16.5 (8)	194 (8)	8	7.91 (8)	111 (8)
			(4.15; 11.0)	(44.0; 231)		(4.39; 18.4)	(44.0; 180)		(4.62; 59.0)	(59.6; 629)		(2.67; 23.4)	(58.7; 208)
	CYD32	22	134 (22)	527 (22)	22	93.6 (22)	585 (22)	22	83.6 (22)	442 (22)	22	21.5 (22)	184 (22)
			(46.6; 385)	(219; 1268)		(32.0; 274)	(330; 1038)		(42.1; 166)	(234; 835)		(11.2; 41.3)	(109; 309)
Endemic LatAm	CYD24	11	155 (11)	716 (11)	11	92.8 (11)	250 (11)	11	139 (11)	530 (11)	11	14.2 (11)	159 (11)
			(42.7; 560)	(394; 1301)		(36.4; 236)	(184; 341)		(40.4; 480)	(266; 1058)		(6.23; 32.4)	(113; 224)

M: number of subjects with available Ab titer for the relevant endpoint

Source: Modified from 5.3.5.3 Integrated Immunogenicity Analysis report, Table 3.9.6.7

Table 30. Geometric means of Dengue PRNT50 antibody (1/dil) pre-Dose 1 and PD3 for each serotype, in seropositive subjects aged 2 to 5 years

			Serotype 1		Serotype 2			Serotype 3			Serotype 4	
Region	Study	N	Pre-dose 1 GM (M) (95% CI)	Post-dose 3 GM (M) (95% CI)	N	Pre-dose 1 GM (M) (95% CI)	Post-dose 3 GM (M) (95% CI)	N	Pre-dose 1 GM (M) (95% CI)	Post-dose 3 GM (M) (95% CI)	N	Pre-dose 1 GM (M) (95% CI)	Post-dose 3 GM (M) (95% CI)
Endemic AP	CYD14	243	42.6 (240)	186 (242)	243	65.4 (242)	363 (242)	243	49.4 (242)	209 (242)	243	25.1 (240)	132 (242)
			(32.2; 56.2)	(150; 232)		(49.9; 85.9)	(304; 434)		(38.6; 63.3)	(171; 255)		(20.4; 30.9)	(113; 154)
	CYD22	24	14.3 (24)	85.0 (24)	24	11.0 (24)	134 (24)	24	44.9 (24)	183 (24)	24	12.2 (24)	108 (24)
			(7.40; 27.5)	(43.5; 166)		(6.21; 19.4)	(81.4; 221)		(23.0; 88.0)	(98.1; 341)		(6.87; 21.8)	(64.4; 181)
	CYD23	14	57.9 (14)	146 (14)	14	68.8 (14)	366 (14)	14	38.2 (14)	304 (14)	14	23.3 (14)	114 (14)
			(15.0; 224)	(48.9; 438)		(15.1; 313)	(182; 734)		(13.4; 109)	(168; 547)		(10.7; 50.7)	(68.4; 189)
	CYD28	9	5.00 (9)	114 (9)	9	8.28 (9)	240 (9)	9	16.4 (9)	201 (9)	9	9.30 (9)	182 (8)
			(NC)	(62.5; 207)		(3.66; 18.7)	(86.6; 668)		(6.09; 44.3)	(83.9; 482)		(4.97; 17.4)	(95.4; 348)
	CYD32	44	24.9 (44)	187 (44)	44	28.2 (44)	205 (44)	44	34.5 (44)	210 (44)	44	15.0 (44)	131 (44)
			(13.2; 47.3)	(123; 282)		(14.4; 55.3)	(137; 308)		(20.8; 57.2)	(147; 302)		(9.09; 24.8)	(99.5; 172)
Endemic LatAm	CYD24	39	102 (39)	475 (34)	39	44.2 (39)	274 (34)	39	98.5 (39)	349 (34)	39	15.3 (39)	363 (34)
			(52.1; 200)	(272; 830)		(27.8; 70.4)	(193; 388)		(54.4; 178)	(220; 554)		(9.17; 25.4)	(244; 540)

M: number of subjects with available Ab titer for the relevant endpoint

Source: Modified from 5.3.5.3 Integrated Immunogenicity Analysis report, Table 3.5.1.3

Overall, a trend towards higher GMTRs of PD3/baseline was observed with decreasing age, being highest in the youngest age group (2 to 5 years). A similar trend was observed in lower endemic settings compared to higher endemic settings.

It is important to highlight that, despite the lower titer levels observed for serotype 4, the GMTRs of PD3/baseline were similar or higher compared to the other serotypes.

In subjects aged 6 to 8 years, GMTRs of PD3/baseline tended to be similar or higher than in subjects 9 to 17 years but lower that those aged 2 to 5 years. GMTRs of PD3/baseline for each serotype in subjects 6 to 8 years ranged from 2.03 for serotype 1 in CYD22 to 9.05 for serotype 3 in CYD28.

The CHMP considered that, overall, pre-Dose 1 GMTs were higher in older subjects than in younger subjects (i.e. GMTs in 9 to 17 years > 6 to 8 years > 2 to 5 years).

Baseline GMTs varied across studies due to, as explained by the MAH, different endemic settings and therefore different natural dengue exposure. Although highly plausible, this interpretation was not supported by a description of the dengue epidemiology of countries at the time of study conduct.

Because of the low number of seropositive subjects included in all the studies, with the exception of study CYD14, the assessment was mainly focused on the PD3 results obtained in the CYD14 study. Higher PD3 nAb titers were observed in the 9-17 year age group when compared to 6-8 years age group. PD3 nAb titers were higher for serotypes 3 and 4 in the 6-8 year age group when compared to 2-5 years age group (although 95%CI were overlapping). In contrast, PD3 nAb titers were similar between both groups for Serotype 1 and Serotype 2, although baseline GMTs were higher in the 6-8 years group when compared to the 2-5 years group. Consequently, GMTRs were higher for the 2-5 years age group when compared to the 6-8 years group.

In all age groups, GMTs tend to be consistently lower for Serotype 4 when compared to Serotypes 1-3 GMTs. Serotype 4 GMTRs were nevertheless roughly similar than Serotypes 1-3 GMTRs.

Data obtained in the 6-8 yoa children included in studies conducted in the Endemic AP regions (pooled analysis) support the findings of CYD14 study.

In the absence of ICP, the clinical relevance of these findings is unknown. Meanwhile, VE was evaluated in study CYD14 for the different age groups.

2.4.3.2. Persistence of immunogenicity

Results presented herein correspond to the assessment of persistence of immunogenicity from efficacy studies (CYD14, CYD15 and CYD23) and supportive long-term follow-up studies (CYD22, CYD28 and CYD65). Antibody persistence (in terms of GMTs) was evaluated each year, for up to 4 years after the last injection in CYD22 and CYD28 and for up to 5 years in pivotal studies CYD14 and CYD15. In CYD23 persistence was assessed 1 year after the last injection. CYD65 includes assessment up to 2 years after the last injections; however, results up to 1 year were available at the time of this addendum.

Results in Seropositive Subjects Aged 9 to 17 Years (3-Dose Schedule)

The number of baseline dengue seropositive subjects aged 9 to 17 years contributing to the evaluation of Ab persistence is presented in the table below.

Table 31. Seropositive subjects aged 9 to 17 years contributing to Ab persistence database by age group - FAS and FASI

		CYD dengue vaccine Group	Control Group
Data available post third injection	**Studies Included**	**9 to 17 Years**	**9 to 17 Years**
1-year after the 3rd injection	**CYD22, CYD28, CYD23, CYD14, CYD15, CYD65**	2232	1041
2-year after the 3rd injection	**CYD22, CYD28, CYD14, CYD15**	2041	992
3-year after the 3rd injection	**CYD22, CYD28, CYD14, CYD15**	1981	954
4-year after the 3rd injection	**CYD22, CYD28, CYD14, CYD15**	1864	901

		CYD dengue vaccine Group	Control Group
Data available post third injection	**Studies Included**	**9 to 17 Years**	**9 to 17 Years**
5-year after the 3rd injection	**CYD14, CYD15**	1625	808

Source: Modified from 5.3.5.3 Integrated Immunogenicity Analysis report, Table 3.9.3.13

As shown in the table below, an overall decline in GMTs for each serotype compared to PD3 GMTs was observed particularly one year after the 3rd injection of the CYD dengue vaccine.

GMTs then reached a plateau and stabilized about 2 years after the third injection. Subsequently, they remained at similar levels or experimented a lesser decrease for each serotype up to 4 years in CYD22 and CYD28, and up to 5 years in CYD14. In CYD14, during Year 3 post-injection 3, there was a slight increase of GMTs for each serotype, particularly for serotype 2. As it was observed in both the CYD dengue vaccine and control group, possibly related to wild type virus circulation.

A similar pattern was observed in both regions; however, in CYD15, an increase in GMTs was observed at 4 years post-injection 3, decreasing, during the last follow-up year (i.e. 5 years post injection 3) to levels comparable to those at 3 years post-injection 3. This increase, observed both in the CYD dengue vaccine and control groups, could be explained by the Zika outbreak that occurred in Latin America and the Caribbean during the 3rd year of CYD15 study follow up given the structural similarities between both dengue and Zika viruses that may result in immunological cross-reactivity.

During the long-term follow-up GMTs for each serotype in the CYD dengue vaccine group remained mostly higher at the yearly time points up to 5 years PD3 compared to baseline values and remained higher than GMTs observed in the control group.

Table 32. Geometric means of Dengue PRNT50 antibody (1/dil) up to 5 years after the last injection for each serotype, in baseline seropositive subjects aged 9 to 17 years - FAS and FASI

		CYD dengue vaccine Group							
Region	Study	N	Pre-dose 1 GM (M) (95% CI)	Post-dose 3 GM (M) (95% CI)	Year 1 GM (M) (95% CI)	Year 2 GM (M) (95% CI)	Year 3 GM (M) (95% CI)	Year 4 GM (M) (95% CI)	Year 5 GM (M) (95% CI)
Serotype 1									
Endemic AP	CYD14	485	167 (481)	437 (482)	394 (471)	340 (474)	344 (471)	288 (469)	243 (465)
			(138; 202)	(373; 511)	(333; 467)	(287; 403)	(289; 410)	(244; 340)	(207; 286)
	CYD22	25	116 (25)	328 (24)	218 (24)	185 (24)	157 (24)	140 (24)	-
			(44.6; 303)	(152; 706)	(101; 468)	(82.5; 415)	(61.6; 401)	(57.0; 345)	-
	CYD23	58	214 (58)	461 (56)	388 (56)	-	-	-	-
			(118; 386)	(259; 819)	(226; 667)	-	-	-	-
	CYD28	31	20.4 (31)	153 (28)	46.4 (27)	29.8 (25)	25.8 (26)	17.7 (24)	-
			(8.81; 47.2)	(69.1; 339)	(18.6; 116)	(11.2; 79.4)	(9.80; 67.7)	(7.23; 43.4)	-
	CYD65	44	76.9 (44)	637 (43)	384 (22)	-	-	-	-
			(43.5; 136)	(404; 1003)	(208; 709)	-	-	-	-
Endemic LatAm	CYD15	1048	278 (1046)	703 (1040)	534 (1013)	414 (980)	477 (947)	783 (859)	503 (838)
			(247; 313)	(634; 781)	(476; 599)	(371; 463)	(426; 534)	(693; 885)	(451; 562)
	CYD65	31	75.2 (31)	280 (30)	150 (27)	-	-	-	-
			(35.6; 159)	(165; 473)	(89.9; 250)	-	-	-	-
Serotype 2									
Endemic AP	CYD14	485	319 (482)	793 (481)	619 (474)	465 (471)	602 (472)	434 (468)	388 (465)
			(274; 373)	(704; 892)	(546; 702)	(408; 531)	(525; 691)	(382; 493)	(341; 441)
	CYD22	25	177 (25)	654 (24)	545 (24)	703 (24)	316 (24)	344 (24)	-
			(90.2; 348)	(349; 1226)	(263; 1126)	(322; 1532)	(162; 615)	(180; 658)	-
	CYD23	58	281 (58)	645 (56)	427 (56)	-	-	-	-
			(164; 479)	(424; 981)	(283; 643)	-	-	-	-
	CYD28	31	48.0 (31)	268 (28)	133 (27)	99.3 (25)	63.1 (26)	76.3 (24)	-
			(19.4; 119)	(134; 536)	(56.0; 318)	(35.3; 279)	(24.2; 164)	(26.2; 223)	-

		CYD dengue vaccine Group							
Region	**Study**	**N**	**Pre-dose 1 GM (M) (95% CI)**	**Post-dose 3 GM (M) (95% CI)**	**Year 1 GM (M) (95% CI)**	**Year 2 GM (M) (95% CI)**	**Year 3 GM (M) (95% CI)**	**Year 4 GM (M) (95% CI)**	**Year 5 GM (M) (95% CI)**
	CYD65	44	125 (44)	678 (43)	717 (22)	-	-	-	-
			(83.7; 187)	(486; 947)	(450; 1143)	-	-	-	-
Endemic LatAm	**CYD15**	1048	306 (1048)	860 (1040)	620 (1015)	563 (981)	523 (946)	629 (859)	463 (838)
			(277; 338)	(796; 930)	(570; 674)	(519; 612)	(482; 568)	(572; 692)	(426; 502)
	CYD65	31	166 (31)	584 (30)	438 (27)	-	-	-	-
			(83.7; 331)	(356; 958)	(286; 669)	-	-	-	-
Serotype 3									
Endemic AP	**CYD14**	485	160 (477)	443 (481)	510 (474)	338 (461)	464 (472)	385 (469)	299 (465)
			(135; 190)	(387; 507)	(444; 586)	(292; 393)	(399; 539)	(335; 443)	(261; 343)
	CYD22	25	68.8 (25)	234 (24)	311 (24)	218 (24)	138 (24)	95.9 (24)	-
			(37.9; 125)	(141; 389)	(162; 597)	(115; 414)	(77.0; 247)	(57.3; 160)	-
	CYD23	58	117 (58)	532 (56)	289 (56)	-	-	-	-
			(71.5; 191)	(350; 810)	(193; 434)	-	-	-	-
	CYD28	31	30.6 (31)	294 (28)	82.3 (27)	93.0 (25)	44.1 (26)	40.4 (23)	-
			(17.5; 53.6)	(175; 495)	(36.3; 186)	(38.9; 222)	(18.8; 104)	(16.1; 101)	-
	CYD65	44	258 (44)	770 (43)	659 (22)	-	-	-	-
			(156; 426)	(507; 1171)	(346; 1253)	-	-	-	-
Endemic LatAm	**CYD15**	1048	261 (1048)	762 (1040)	503 (1016)	505 (979)	525 (947)	641 (859)	539 (838)
			(235; 289)	(699; 830)	(457; 554)	(462; 551)	(479; 577)	(579; 709)	(493; 589)
	CYD65	31	151 (31)	393 (30)	324 (27)	-	-	-	-
			(67.7; 339)	(228; 677)	(183; 573)	-	-	-	-
Serotype 4									
Endemic AP	**CYD14**	485	83.8 (483)	272 (481)	192 (476)	163 (461)	209 (470)	178 (469)	130 (465)
			(72.0; 97.6)	(245; 302)	(172; 213)	(145; 182)	(188; 234)	(160; 198)	(115; 146)
	CYD22	25	39.8 (25)	254 (24)	175 (24)	112 (24)	82.1 (24)	46.0 (24)	-
			(21.3; 74.6)	(147; 440)	(107; 284)	(66.2; 188)	(56.1; 120)	(28.4; 74.7)	-
	CYD23	58	81.2 (58)	231 (56)	341 (56)	-	-	-	-
			(51.0; 129)	(183; 293)	(221; 525)	-	-	-	-
	CYD28	31	13.1 (31)	209 (28)	103 (27)	95.4 (25)	79.8 (26)	81.0 (24)	-
			(7.76; 22.1)	(155; 282)	(70.9; 149)	(52.2; 174)	(51.7; 123)	(50.1; 131)	-
	CYD65	44	64.2 (44)	434 (43)	191 (22)	-	-	-	-
			(42.3; 97.3)	(319; 590)	(131; 280)	-	-	-	-
Endemic LatAm	**CYD15**	1048	73.3 (1046)	306 (1040)	238 (1016)	189 (981)	225 (946)	269 (859)	190 (838)
			(66.6; 80.7)	(286; 328)	(221; 256)	(176; 203)	(211; 241)	(247; 293)	(177; 204)
	CYD65	31	64.7 (31)	376 (30)	192 (27)	-	-	-	-
			(29.0; 144)	(230; 612)	(122; 303)	-	-	-	-

M: number of subjects with available Ab titer for the relevant endpoint
For CYD65, only Group 1 included
Source: Modified from 5.3.5.3 Integrated Immunogenicity Analysis Report, Table 3.9.3.9 to Table 3.9.3.12

Results in Seropositive Subjects Aged 9 to 17 Years

Results of persistence of immunogenicity from efficacy studies CYD14, CYD15 and CYD23 as well as from supportive long-term follow-up studies CYD22, CYD28 and CYD65 were presented. Antibody persistence was evaluated in terms of GMTs for up to 4 years after the last injection in CYD22 and CYD28 and up to 5 years in pivotal studies CYD14 and CYD15. In CYD23 and CYD65, persistence results are presented 1 year after the last injection.

The CHMP considered that all relevant studies were included in this analysis. However, results of CYD14 study are the only ones that can be compared between age groups. CYD22, CYD23 and CYD28 studies included different age range groups but the number of subjects were limited and therefore results interpretation is not warranted. No results for studies conducted in LatAm are available for the 6-8 and 2-5 years age groups.

The number of 'loss of FU' was limited in most of the studies and 97% of the CYD14 subjects were followed up to Year 5 (n=481 pre-D1 and n=465 post-5Y).

Ab persistence data interpretation is complicated by the variable serotype-specific vaccine-induced immune responses and also by, as mentioned by the MAH, the probable occurrence of wild type virus circulation during the Year 3 in countries where study CYD14 was conducted. GMTs observed in the control group at Year 3 were higher than at baseline but similar than at Year 1, which might also suggest a (more intense) virus circulation during the first year following vaccination, in one or more countries were the study was conducted. These findings suggest than the GMTs at Year 1 observed in the vaccinees group might be overestimated and that a more marked decrease would have been observed. This is consistent with the absence of Serotype 3-GMTs decrease during the first year following vaccination and the overall higher GMTs decrease observed at Year 1 in study CYD15.

Overall, there was a trend for decreased GMTs against all 4 serotypes from PD3 through Year 5. Of note, GMTs for each serotype remained at higher levels than those observed at baseline in all age groups.
GMTs at Year 5 in the vaccinated group were higher, for each serotype, than in the control group.
The effect of the possible virus circulation during the study conduct on the serotype-specific immune response at Year 5 and over a longer period is not known. Ab persistence in vaccinated subjects living outside endemic countries is therefore not known.

In the absence of ICP, the clinical relevance of these findings is unknown.

GMTs for each serotype observed in CYD15 study also tend to decrease over years. However, as mentioned by the MAH, a ZIKA outbreak occurred during Year 4, therefore no firm conclusion on Ab persistence up to Year 5 can be drawn. Results observed at Year 4 might be due to immunological cross-reactivity (See efficacy assessment).

Results in Seropositive Subjects Aged 6 to 8 Years

The number baseline dengue seropositive subjects aged 6 to 8 years contributing to the evaluation of Ab persistence is presented in the table below.

Table 33. Seropositive subjects aged 6 to 8 years contributing to Ab persistence database - FAS and FASI

Data available post third injection	Studies Included	CYD dengue vaccine Group	Control Group
1-year after the 3rd injection	CYD22, CYD28, CYD23, CYD14	410	203
2-year after the 3rd injection	CYD22, CYD28, CYD14	317	150
3-year after the 3rd injection	CYD22, CYD28, CYD14	319	148
4-year after the 3rd injection	CYD22, CYD28, CYD14	317	148
5-year after the 3rd injection	CYD14	247	122

Source: Modified from 5.3.5.3 Integrated Immunogenicity Analysis report, Table 3.9.5.13

All data for the analysis of the individuals aged 6 to 8 years come from studies conducted in the Asia Pacific endemic region. An overall decline in GMTs for each serotype compared to PD3 GMTs was observed over the 2 years after the third dose. GMTs then stabilized or slightly decreased for each serotype up to 4 years in CYD22 and CYD28, and up to 5 years in CYD14 after the 3rd vaccine injection. The slight increase in GMTs observed in subjects aged 9 to 17 years from CYD14 during the 3rd year post-injection 3 was also observed in subjects aged 6 to 8 years.

During the long-term follow up GMTs for each serotype in the CYD dengue vaccine group remained overall, at higher levels than those observed at baseline and remained higher than or similar (serotype 1) to GMTs observed in the control group.

Overall, Ab persistence up to 5 years in seropositive subjects aged 6 to 8 years followed a similar pattern to that observed in subjects aged 9 to 17 years.

Table 34. Geometric means of Dengue PRNT50 antibody (1/dil) up to 5 years after the last injection for each serotype, in baseline seropositive subjects aged 6 to 8 years - FAS and FASI

CYD dengue vaccine Group									
Region	Study	N	Pre-dose 1 GM(M) (95% CI)	Post-dose 3 GM(M) (95% CI)	Year 1 GM(M) (95% CI)	Year 2 GM(M) (95% CI)	Year 3 GM(M) (95% CI)	Year 4 GM(M) (95% CI)	Year 5 GM(M) (95% CI)
Serotype 1									
Endemic AP	CYD14	168	80.8 (167)	203 (166)	149 (164)	113 (164)	134 (168)	123 (168)	94.4 (164)
			(57.3; 114)	(154; 268)	(108; 205)	(80.8; 159)	(97.2; 186)	(89.8; 168)	(69.6; 128)
	CYD22	17	47.3 (17)	133 (15)	136 (14)	79.7 (14)	88.4 (14)	60.7 (14)	-
			(13.6; 164)	(51.3; 343)	(39.2; 473)	(22.8; 279)	(24.2; 323)	(15.4; 240)	-
	CYD23	66	66.5 (66)	213 (63)	224 (63)	-	-	-	-
			(39.4; 112)	(138; 329)	(134; 374)	-	-	-	-
	CYD28	8	6.75 (8)	101 (8)	17.5 (8)	14.6 (8)	15.8 (8)	11.6 (8)	-
			(4.15; 11.0)	(44.0; 231)	(6.62; 46.2)	(5.19; 41.3)	(4.93; 50.7)	(4.34; 31.0)	-
Serotype 2									
Endemic AP	CYD14	168	118 (168)	369 (166)	264 (165)	179 (166)	269 (168)	198 (168)	171 (164)
			(86.0; 161)	(298; 457)	(209; 333)	(143; 224)	(208; 349)	(153; 256)	(132; 223)
	CYD22	17	41.8 (17)	147 (15)	152 (14)	117 (14)	135 (14)	87.8 (14)	-
			(16.2; 108)	(74.0; 292)	(56.2; 412)	(38.8; 351)	(37.9; 483)	(26.4; 293)	-
	CYD23	66	118 (66)	548 (63)	338 (63)	-	-	-	-
			(69.0; 202)	(355; 844)	(209; 545)	-	-	-	-
	CYD28	8	8.97 (8)	89.0 (8)	27.7 (8)	20.6 (8)	18.5 (8)	19.5 (8)	-
			(4.39; 18.4)	(44.0; 180)	(9.99; 76.9)	(7.74; 55.1)	(5.21; 65.6)	(4.39; 86.5)	-
Serotype 3									
Endemic AP	CYD14	168	105 (168)	316 (166)	342 (165)	181 (161)	217 (168)	197 (168)	177 (164)
			(75.5; 145)	(244; 411)	(260; 449)	(136; 241)	(158; 298)	(150; 258)	(136; 231)
	CYD22	17	44.2 (17)	135 (15)	163 (14)	113 (14)	121 (14)	37.8 (14)	-
			(20.5; 95.3)	(76.8; 237)	(67.0; 398)	(50.0; 255)	(42.7; 345)	(15.5; 92.3)	-
	CYD23	66	49.5 (66)	462 (63)	202 (63)	-	-	-	-
			(34.8; 70.5)	(328; 651)	(133; 307)	-	-	-	-
	CYD28	8	16.5 (8)	194 (8)	86.1 (8)	54.0 (8)	43.6 (8)	24.6 (7)	-
			(4.62; 59.0)	(59.6; 629)	(27.4; 270)	(8.73; 334)	(8.91; 214)	(4.43; 136)	-
Serotype 4									
Endemic AP	CYD14	168	48.4 (168)	175 (166)	102 (164)	72.3 (162)	116 (168)	106 (168)	80.8 (164)
			(37.2; 63.0)	(145; 211)	(80.5; 130)	(57.2; 91.4)	(90.8; 148)	(85.0; 133)	(64.4; 101)
	CYD22	17	16.0 (17)	134 (15)	101 (14)	41.7 (14)	66.5 (14)	29.7 (14)	-
			(8.32; 30.9)	(95.0; 190)	(62.1; 164)	(22.8; 76.2)	(32.5; 136)	(16.2; 54.3)	-

CYD dengue vaccine Group									
Region	Study	N	Pre-dose 1 GM(M) (95% CI)	Post-dose 3 GM(M) (95% CI)	Year 1 GM(M) (95% CI)	Year 2 GM(M) (95% CI)	Year 3 GM(M) (95% CI)	Year 4 GM(M) (95% CI)	Year 5 GM(M) (95% CI)
	CYD23	66	53.8 (66)	195 (63)	211 (63)	-	-	-	-
			(35.2; 82.2)	(141; 269)	(144; 308)	-	-	-	-
	CYD28	8	7.91 (8)	111 (8)	37.0 (8)	38.2 (8)	35.4 (8)	28.2 (8)	-
			(2.67; 23.4)	(58.7; 208)	(11.9; 116)	(10.1; 144)	(8.86; 141)	(7.58; 105)	-

M: number of subjects with available Ab titer for the relevant endpoint
Source: Modified from 5.3.5.3 Integrated Immunogenicity Analysis report, Table 3.9.6.9, to 3.9.6.12

Results in Seropositive Subjects Aged 6 to 8 Years

Results of persistence of immunogenicity from efficacy studies CYD14 and CYD23 as well as from supportive long-term follow-up studies CYD22 and CYD28, all conducted in AP region, were presented. Antibody persistence was evaluated in terms of GMTs for up to 4 years after the last injection in CYD22 and CYD28 and up to 5 years in pivotal study CYD14. In CYD23, Ab persistence results are presented 1 year after the last injection. No LatAm study results were presented.

The CHMP considered that, in studies CYD22 and CYD28, very few vaccinated subjects were included, i.e. n=17 and n=8 respectively. Sample size of study CYD23 was also limited (n vaccinees=66). Assessment was therefore mainly focused on CYD14 study data. The number of 'loss of FU' was limited in most of the studies and 98% of the CYD14 subjects were followed up to Year 5 (n=168 pre-D1 and n=164 post-5Y).
Overall, Ab persistence up to 5 years in seropositive subjects aged 6 to 8 years followed a similar pattern to that observed in subjects aged 9 to 17 years. GMTs observed at Year 5 were lower in the 6-8 years when compared to the 9-17 years age groups. GMTs at Year 5 were higher in the vaccinated group, for each serotype, than in the control group. For the 6 to 8 years aged control group, as for the vaccinated group, similar pattern of GMTs than in subjects aged 9 to 17 years was observed.

In the absence of ICP, the clinical relevance of these findings is unknown.

Results in Seropositive Subjects Aged 2 to 5 Years

The table below present the number of subjects of this age group contributing to long term persistence.

Table 35. Seropositive subjects aged 2 to 5 years contributing to Ab persistence database - FAS and FASI

Data available post third injection	Studies Included	CYD dengue vaccine Group	Control Group
1-year after the 3rd injection	CYD22, CYD28, CYD23, CYD14	559	259
2-year after the 3rd injection	CYD22, CYD28, CYD14	522	250
3-year after the 3rd injection	CYD22, CYD28, CYD14	522	249

Data available post third injection	Studies Included	CYD dengue vaccine Group	Control Group
4-year after the 3rd injection	**CYD22, CYD28, CYD14**	520	245
5-year after the 3rd injection	**CYD14**	439	215

Source: Modified from 5.3.5.3 Integrated Immunogenicity Analysis report, Table 3.7.3.4

All data for the analysis of the individuals aged 2 to 5 years come from studies conducted in the Asia Pacific endemic region. As illustrated in the table below, one year after the 3rd injection of the CYD dengue vaccine, an overall decline in GMTs for each serotype compared to PD3 GMTs was observed. However, values remained overall higher compared to baseline.

Individuals aged 2 to 5 years showed lower baseline, PD3 GMTs and showed a more pronounced decrease of GMTs compared to those aged 6 to 8 years.

Table 36. Geometric means of Dengue PRNT50 antibody (1/dil) up to 5 years after the last injection for each serotype, in baseline seropositive subjects aged 2 to 5 years - FAS and FASI

CYD dengue vaccine Group									
Region	Study	N	Pre-dose 1 GM(M) (95% CI)	Post-dose 3 GM(M) (95% CI)	Year 1 GM(M) (95% CI)	Year 2 GM(M) (95% CI)	Year 3 GM(M) (95% CI)	Year 4 GM(M) (95% CI)	Year 5 GM(M) (95% CI)
Serotype 1									
Endemic AP	CYD14	243	42.6 (240)	186 (242)	104 (236)	89.6 (235)	99.2 (240)	93.3 (238)	72.2 (238)
			(32.2; 56.2)	(150; 232)	(79.1; 137)	(67.8; 118)	(76.3; 129)	(72.3; 120)	(55.6; 93.6)
	CYD22	24	14.3 (24)	85.0 (24)	60.1 (24)	32.6 (23)	13.5 (23)	20.0 (23)	-
			(7.40; 27.5)	(43.5; 166)	(26.7; 135)	(16.1; 66.1)	(6.16; 29.5)	(8.61; 46.4)	-
	CYD23	14	57.9 (14)	146 (14)	110 (14)	-	-	-	-
			(15.0; 224)	(48.9; 438)	(38.4; 316)	-	-	-	-
	CYD28	9	5.00 (9)	114 (9)	27.4 (9)	26.1 (9)	6.41 (9)	5.51 (9)	-
			(NC)	(62.5; 207)	(10.4; 72.3)	(9.21; 74.0)	(3.61; 11.4)	(4.40; 6.90)	-
Serotype 2									
Endemic AP	CYD14	243	65.4 (242)	363 (242)	172 (239)	145 (231)	204 (240)	148 (238)	131 (238)
			(49.9; 85.9)	(304; 434)	(140; 210)	(115; 182)	(162; 257)	(117; 188)	(104; 164)
	CYD22	24	11.0 (24)	134 (24)	42.4 (24)	33.7 (23)	19.2 (23)	21.0 (23)	-
			(6.21; 19.4)	(81.4; 221)	(21.7; 83.0)	(16.3; 69.4)	(9.43; 39.2)	(9.83; 44.8)	-
	CYD23	14	68.8 (14)	366 (14)	114 (14)	-	-	-	-
			(15.1; 313)	(182; 734)	(41.7; 312)	-	-	-	-
	CYD28	9	8.28 (9)	240 (9)	44.7 (9)	33.1 (9)	11.5 (9)	14.3 (9)	-
			(3.66; 18.7)	(86.6; 668)	(14.5; 138)	(8.51; 128)	(3.82; 34.3)	(5.01; 40.8)	-
Serotype 3									
Endemic AP	CYD14	243	49.4 (242)	209 (242)	164 (236)	115 (225)	145 (239)	145 (238)	98.8 (238)
			(38.6; 63.3)	(171; 255)	(130; 207)	(89.4; 147)	(112; 187)	(115; 184)	(78.2; 125)
	CYD22	24	44.9 (24)	183 (24)	44.8 (24)	42.8 (23)	33.8 (23)	32.0 (23)	-
			(23.0; 88.0)	(98.1; 341)	(21.9; 91.4)	(20.1; 91.3)	(15.1; 75.6)	(14.7; 69.4)	-
	CYD23	14	38.2 (14)	304 (14)	78.5 (14)	-	-	-	-
			(13.4; 109)	(168; 547)	(38.3; 161)	-	-	-	-
	CYD28	9	16.4 (9)	201 (9)	43.9 (9)	74.8 (9)	10.4 (9)	11.9 (8)	-
			(6.09; 44.3)	(83.9; 482)	(12.7; 151)	(15.5; 360)	(4.24; 25.3)	(5.18; 27.3)	-
Serotype 4									

CYD dengue vaccine Group									
Region	Study	N	Pre-dose 1 GM(M) (95% CI)	Post-dose 3 GM(M) (95% CI)	Year 1 GM(M) (95% CI)	Year 2 GM(M) (95% CI)	Year 3 GM(M) (95% CI)	Year 4 GM(M) (95% CI)	Year 5 GM(M) (95% CI)
Endemic AP	CYD14	243	25.1 (240)	132 (242)	72.2 (237)	58.3 (229)	76.5 (240)	66.3 (238)	52.2 (238)
			(20.4; 30.9)	(113; 154)	(60.3; 86.3)	(47.6; 71.4)	(63.5; 92.1)	(54.8; 80.3)	(42.9; 63.5)
	CYD22	24	12.2 (24)	108 (24)	41.5 (24)	33.5 (23)	20.9 (23)	17.1 (23)	-
			(6.87; 21.8)	(64.4; 181)	(24.6; 69.9)	(20.7; 54.2)	(13.9; 31.2)	(10.6; 27.8)	-
	CYD23	14	23.3 (14)	114 (14)	81.8 (14)	-	-	-	-
			(10.7; 50.7)	(68.4; 189)	(48.0; 139)	-	-	-	-
	CYD28	9	9.30 (9)	182 (8)	36.9 (9)	17.5 (9)	12.8 (9)	11.8 (9)	-
			(4.97; 17.4)	(95.4; 348)	(16.3; 83.4)	(6.67; 45.7)	(5.25; 31.1)	(6.29; 22.3)	-

M: number of subjects with available Ab titer for the relevant endpoint
Source: Modified from 5.3.5.3 Integrated Immunogenicity Analysis report, Table 3.5.5.1 to 3.5.5.4

Results in Seropositive Subjects Aged 2 to 5 Years

Results of persistence of immunogenicity from efficacy studies CYD14 and CYD23 as well as from supportive long-term follow-up studies CYD22 and CYD28, all conducted in the AP region, were presented. Antibody persistence was evaluated in terms of GMTs for up to 4 years after the last injection in CYD22 and CYD28 and up to 5 years in pivotal study CYD14. In CYD23, Ab persistence results are presented 1 year after the last injection. No LatAm study results were presented.

The CHMP considered that, in studies CYD22, CYD23 and CYD28, very few vaccinated subjects were included, i.e. n=24, n=14 and n=9 respectively. As for the other age groups, assessment was mainly focused on CYD14 study data.

The number of 'loss of FU' was limited in most of the studies and 99% of the CYD14 subjects were followed up to Year 5 (n=240 pre-D1 and n=238 post-5Y).

Overall, Ab persistence up to 5 years in seropositive subjects aged 2 to 5 years followed a similar pattern to that observed in subjects aged 6 to 8 and 9 to 17 years. GMTs at Year 5 were higher in the vaccinated group, for each serotype, than in the control group. GMTs observed at Year 5 were lower in the 2-5 years when compared to the 6-8 years age groups.

In the absence of ICP, the clinical relevance of these findings is unknown.

2.4.4. Discussion on clinical immunogenicity

Overall design and immunogenicity methods

The integrated immunogenicity analysis included results of 12 studies, i.e. two large-scale pivotal efficacy studies CYD14 and CYD15, and 10 supportive studies CYD13, CYD22, CYD24, CYD28, CYD30, CYD65 (Phase 2 studies), CYD23 (Phase 2b), CYD32 (Phase 3) and CYD71 and CYD67 (Phase 3b, co-administration studies).

All 12 clinical trials were conducted in healthy subjects (2-50 yoa) in endemic regions (Asia Pacific and Latin America and the Caribbean) and are consistent in terms of the general study design, vaccine formulation and schedule. Although twelve studies were included in the integrated immunogenicity analysis, only 6 of them included children from 2-8 yoa.

The design of most of the individual studies was already assessed at initial MAA and deemed appropriate. The laboratory was blinded to the treatment group when performing all testing. The FU duration varied across studies. It is considered that all relevant studies were included in this analysis.
Dengue immunogenicity was evaluated based on PRNT50 results. The validated assay was the core immunologic assay for measuring functional antibodies able to neutralize dengue virus in studies submitted at the initial MAA. The assay methodology is in line with WHO recommendation and was deemed acceptable although specificity might not be optimal due to cross-reactivity with other flaviviruses.

The dengue serostatus at baseline was defined as previously, i.e. seropositive if the PRNT50 titre was ≥ 10 against at least one serotype, and seronegative if PRNT50 titre was < lower limit of quantification (LLOQ) against any of the four dengue serotypes in the baseline sample.

Analysis were performed on the full analysis set (FAS) or the FAS for the immunogenicity subset (FASI), as appropriate. The FAS was defined as all subjects who received at least one injection of the CYD dengue vaccine or control vaccine, and who had at least 1 blood sample drawn and 1 valid post-injection serology result. In studies in which only a subset of subjects was followed-up for immunogenicity (i.e. CYD14, CYD15, CYD23, CYD28), the FASI was defined as described for the FAS.

The main objective of the integrated immunogenicity analysis was to provide an overview of the humoral immune response against each dengue serotype induced by the CYD dengue vaccine, according to age and region, in baseline dengue seropositive subjects, with a focus on the response 28 days PD3. Other objectives were to provide an overview of the persistence of the humoral immune response to the CYD dengue vaccine using baseline, 28 days PD3, and yearly PD3 time points, according to age group and region, in baseline seropositive subjects, using data collected from the pivotal and supportive studies with LTFUs.

Results were compared between age ranges of 2-5, 6-8 and 9-17 which is appropriate; VE results presented at initial MAA suggested that children <9 yoa, and particularly children 6-8 yoa, may benefit from vaccination.

Analyses were not pooled between both endemic regions (AP and LatAm) which is deemed appropriate because of difference in epidemiology, in age range, and in YF/JE vaccination status. Results could be expected to be study- and population-related. Results were presented by study to give an overview of the GMTs range, but were also presented pooled for the Endemic AP region for the 6-8 yoa children. Data of this pooled analysis support the findings observed in the main CYD14 study that are presented in the SmPC.

Results

1. Comparison and Analyses of Results Across Studies

Although twelve studies were included in the integrated immunogenicity analysis, results of only 6 of them allow comparison of Pre-D1 and PD3 data by age strata, since CYD65, CYD67, CYD13, CYD15, CYD30 and CYD71 did not include children from 2-8 yoa.

Several studies included only very few seropositive subjects, particularly in the 2-5 and 6-8 years age groups, either in the vaccine or control groups or in both groups. Children 6-8 years are nearly exclusively from AP countries (as are children from 2-5 years), while children 9-17 are from both regions, although mainly from LatAm. Due to this limited number of included subjects result interpretation is difficult in some studies. An imbalance in gender was observed between vaccine and placebo groups in certain studies. Mean age was generally well balanced between both groups in each of the studies.

All studies were conducted in endemic regions. The proportion of baseline dengue seropositive subjects increased with age, which is consistent with the dengue epidemiology and the observation made during the initial MAA. Seropositivity rates at baseline were overall well balanced between vaccine and control groups and ranged between 47.5%-49.2% for 2 to 5 years, 55.4%-62.0% for 6 to 8 years, and 70.3%-74.4% for 9 to 17 years.

Overall, pre-D1 GMTs were higher in older subjects than in younger subjects (i.e. GMTs in 9 to 17 years > 6 to 8 years > 2 to 5 years). Baseline GMTs varied across studies due to, as explained by the MAH, different endemic settings and therefore different natural dengue exposure. Although highly plausible, this interpretation was not supported by a description of the dengue epidemiology of countries at the time of study conduct.

Because of the low number of seropositive subjects included in all the studies, with the exception of study CYD14, the assessment was mainly focused on the PD3 results obtained in the CYD14 study. Higher PD3 nAb titers were observed in the 9-17 year age group when compared to 6-8 years age group. PD3 nAb titers were higher for serotypes 3 and 4 in the 6-8 year age group when compared to 2-5 years age group (although 95%CI were overlapping). In contrast, PD3 nAb titers were similar between both groups for Serotype 1 and Serotype 2, although baseline GMTs were higher in the 6-8 years group when compared to the 2-5 years group. Consequently, GMTRs were higher for the 2-5 years age group when compared to the 6-8 years group. In all age groups, GMTs tend to be consistently lower for Serotype 4 when compared to Serotypes 1-3 GMTs. Serotype 4 GMTRs were nevertheless roughly similar than Serotypes 1-3 GMTRs.

In the absence of ICP, the clinical relevance of these findings is unknown. Meanwhile, VE was evaluated in study CYD14 for the different age groups. VE against VCD due to serotypes 1 and 2 tend to be lower than for serotypes 3 and 4 for which is not consistent with the immunogenicity findings.

The MAH proposes to update the SmPC with baseline and PD3 immunogenicity data observed in seropositive subjects included in the CYD14 study. Since, the data of the pooled analysis for 6-8 yoa children included in studies conducted in AP regions support the findings of study CYD14, this is endorsed.

2. Ab persistence

Results of persistence of immunogenicity from efficacy studies CYD14, CYD15 and CYD23 as well as from supportive long-term follow-up studies CYD22, CYD28 and CYD65 were presented. Antibody persistence was evaluated in terms of GMTs for up to 4 years after the last injection in CYD22 and CYD28 and up to 5 years in pivotal studies CYD14 and CYD15. In CYD23 and CYD65, persistence results are presented 1 year after the last injection.

As mentioned earlier, it is considered that all relevant studies were included in this analysis. However, results of CYD14 study are the only ones that can be compared between age groups because (i) No LatAm study results for children aged 2-8 years were presented, and (ii) although including different age range groups, because of the limited number of subjects included in CYD22, CYD23 and CYD28 studies, results interpretation was not warranted.

The number of 'loss of FU' was limited in most of the studies and 97-99% of the CYD14 subjects were followed up to Year 5.

Overall, Ab persistence up to 5 years in seropositive subjects aged 2 to 5, 6 to 8 and 9-17 years followed a similar pattern. A trend for a decrease in GMTs against all 4 serotypes from PD3 through Year 5 was observed. GMTs for each serotype remained at higher levels than those observed at baseline in all age groups and were higher compared to those observed in the control groups (any age). GMTs observed at

Year 5 were lower in the 2-5 years when compared to the 6-8 years, and in the 6-8 years when compared to the 9-17 years age groups.

Ab persistence data interpretation is complicated by the variable serotype-specific vaccine-induced immune responses and also by the wild type virus circulation during the CYD14 study conduct. GMT result observed in the control group suggest a possible (more intense) virus circulation not only during the Year 3 but also during the Year 1, in one or more countries were the study was conducted. Therefore, the GMTs at Year 1 observed in the vaccinees group might be overestimated and a more marked decrease would have been observed in absence of such virus circulation. Circulation of other pathogens might also influence the duration and magnitude of Ab titers; An increase in Ab titers was observed at Year 4 in study CYD15, which corresponded to the occurrence of ZIKA outbreak (9-17 yoa subjects).

The MAH further investigated the effects of Zika infection on dengue-neutralizing antibody responses in a post-hoc analysis of data from the CYD15 study (Zambrano 2021). Serologically suspected Zika was detected in nearly half of the participants who had a sample at Year 4.

In the placebo group, dengue-neutralizing antibody levels increased between pre- and post-Zika period in those who had serological evidence of Zika, for all serotypes. In the vaccine group, dengue-neutralizing antibody levels increased to a lesser extend for serotype 1 and 3, and did not increase for serotype 2 and 4.

Therefore, while dengue ab levels were higher in the vaccinated vs. placebo subjects before the Zika outbreak for all serotypes, it was not the case after the Zika outbreak anymore in those with evidence of Zika infection. For these subjects, in contrast with the pre-Zika period, after the Zika outbreak, the level of dengue neutralizing antibody achieved in the placebo was similar compared to the vaccinated group (overlapping 95% CIs), except for serotype 4 were it was still higher in the vaccinated..

The impact of immunological cross-reactivity between assay on the results is not clear.

In those without evidence of Zika infection, dengue neutralizing antibodies are still higher in the vaccinated vs. placebo subjects after the Zika outbreak.

As the Zika infection attack rate was substantial during Year 4, this affected the overall level of neutralizing antibodies during Year 4 (and Year 5).

The effect of the possible virus circulation on the serotype-specific immune response at Year 5 and over a longer period is not known. Ab persistence in vaccinated subjects living outside endemic countries is therefore not known.

In the absence of ICP, the clinical relevance of these findings is unknown. Similarly to immunogenicity, the persistence of efficacy in vaccinated subjects living outside endemic countries is neither not known.

2.4.5. Conclusions on clinical immunogenicity

There are limited data on immune response 1 month following vaccination in 6-8 yoa children. These data, from the main study CYD14, indicate that, higher PD3 nAb titers were observed in the 9-17 years age group when compared to 6-8 years age group. PD3 nAb titers were also higher for serotypes 3 and 4 in the 6-8 year age group when compared to 2-5 years age group (although 95%CI were overlapping). In contrast, PD3 nAb titers were similar between both groups for Serotype 1 and Serotype 2, although baseline GMTs were higher in the 6-8 years group when compared to the 2-5 years group.

In all age groups, GMTs tend to be consistently lower for serotype 4 when compared to serotypes 1-3 GMTs. Meanwhile, VE was evaluated in study CYD14 for the different age groups. VE against VCD due to serotypes 1 and 2 were lower than for serotypes 3 and 4 for which is not consistent with the

immunogenicity findings.

Overall, a trend for a decrease in GMTs against all 4 serotypes from PD3 through Year 5 was observed in seropositive subjects aged 2 to 5, 6 to 8 and 9-17 years. GMTs observed at Year 5 were lower in the 2-5 years when compared to the 6-8 years, and in the 6-8 years when compared to the 9-17 years age groups. GMTs for each serotype remained at higher levels than those observed at baseline in all age groups.

The effect of the possible virus (dengue and/or other flaviviruses) circulation during study conduct on the serotype-specific immune response at Year 5 and over a longer period is not known. Ab persistence in vaccinated subjects living outside endemic countries is therefore not known.

In the absence of ICP, the clinical relevance of these findings is unknown.

2.5. Update of the Product information

With this variation, the MAH applied for an extension of the approved indication (SmPC section 4.1) to include children 6 to 8 years of age dengue seropositive at baseline (new text is shown as **bold underlined** and deleted text marked as strikethrough):

*Dengvaxia is indicated for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in individuals ~~9~~ **6** to 45 years of age with prior dengue virus infection and living in endemic areas.*

As a consequence of this change in indications in Section 4.1, Sections 4.2, 4.8 and 5.1 of the SmPC were also updated.

The Package Leaflet has been updated accordingly.

Furthermore, instructions for the installation of the needle were added in the SmPC (Section 6.6) and the Package Leaflet of the single-dose presentation, as follows:

*Attach a sterile needle to the pre-filled syringe for the transfer of the solvent. **The needle must be fitted firmly to the syringe, rotating it by a one-quarter turn.***

2.5.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable. Proposed new text is in line with the latest QRD template, written in a language understandable by the patient and does not impact the design and layout of the Package Leaflet. In addition, given the age range of the proposed added population in this application (6 to 8 years old children), the Package Leaflet is intended to be used by the parents and/or caregivers.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

In the EU, at the time of this variation application, Dengvaxia was indicated *for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in individuals **9** to 45 years of age with prior dengue virus infection and living in endemic areas*.

The MAH seeks to extend the indication to include also children 6-8 years of age.

The proposed indication is: *'Dengvaxia is indicated for the prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in individuals **6** to 45 years of age with prior dengue virus infection and living in endemic areas.'*

The current vaccination schedule consists of 3 injections 6-month apart.

Dengue is an acute, systemic viral infection caused by a virus transmitted primarily by the *Aedes aegypti* mosquito bites. The infection may be asymptomatic, cause flu-like illness, and can develop into a potentially lethal complication called severe dengue (including dengue hemorrhagic fever [DHF]/dengue shock syndrome [DSS]). According to CDC, an estimated 1 in 4 dengue virus infections are symptomatic. Symptomatic dengue virus infection most commonly presents as a mild to moderate, nonspecific, acute febrile illness. Approximately 1 in 20 patients with dengue virus disease progress to develop severe dengue. Severe dengue is a potentially fatal complication, due to plasma leaking, fluid accumulation, respiratory distress, severe bleeding, or organ impairment. Dengue shock syndrome (DSS) is the most severe form of dengue disease and results from hypovolaemia caused by vascular leakage.

There are 4 types of closely related but antigenically distinct dengue virus serotypes (1, 2, 3, and 4). Primary dengue virus infection is thought to provide lifelong protection against the infecting serotype and transient cross-protection against heterologous serotypes. Dengue haemorrhagic fever and dengue shock syndrome occur mostly in individuals during secondary dengue virus infection with a different serotype. Increased risk in secondary infection is thought to be linked to antibody-dependent enhancement of virus infection in Fc receptor–bearing cells and the generation of a large infected cell mass in vivo The antibody-mediated enhancement of dengue seems to be related with the presence of suboptimal neutralizing heterotypic antibodies (that accelerate the rate of internalization of the virus and infection of host cells), and may also be related to the presence of memory T cells with low affinity for the present infecting virus but high affinity for previous infecting serotype(s).

Dengue is the most common mosquito-borne viral disease in humans, spreading globally during the past 30 years as a result of changes in human ecology. The rapidly expanding global footprint of dengue inflicts a significant public health, economic and social burden on the populations of endemic areas. Half of the world's population is now considered at risk of infection by the dengue viruses. Dengue disease is a public health concern in more than 128 countries, with the four dengue virus serotypes found in tropical and sub-tropical regions, including some European territories. Dengue is endemic in Asia, the Pacific area, Africa, and Latin America (including the Caribbean). Sustained transmission of dengue fever does not naturally occur in continental Europe, though sporadic autochthonous dengue cases had been reported in Croatia in 2010 and in France in 2010, 2013, 2014, and 2015, even if more limited. Dengue, however, is endemic in the overseas territories of some European countries such as France (French Guiana, Martinique, and Guadeloupe).

3.1.2. Available therapies and unmet medical need

There is no specific treatment for dengue disease. The management of dengue disease is supportive, with control of fever and pain with antipyretics/analgesics, and adequate fluid intake. Supportive intensive care and fluid management are the mainstays of therapy for severe disease.

Up to the end of 2015, the only available prevention of dengue by vector control has proven to be of limited success, very difficult to sustain and costly. Vaccination provides an alternative in disease control measures. The only vaccine currently on the market is Dengvaxia.

Dengue disease affects all age groups. The age distribution of infected individuals varies between countries. For example, incidence rates were highest in adults in Mexico, Malaysia, and in the French Caribbean, highest in adolescents in Brazil and Thailand, and highest in children in the Philippines and Colombia. Additionally, the population at highest risk can shift over time, as was observed in Colombia and Thailand over the last decade.

Similarly to adults, children experiencing a secondary dengue infection have a much higher risk of developing severe dengue. Children are however at a higher risk of severe dengue. Young children in particular may be less able than adults to compensate for capillary leakage and are consequently at greater risk of dengue shock. National surveillance data from Asian countries show that infants under 1 year of age and children aged 4–9 years have consistently been at the highest risk for severe dengue disease (Guzman 2002, Verhagen 2014), underlying the need to vaccinate children below 9 yoa.

3.1.3. Main clinical studies

The MAH presented integrated analyses of efficacy, immunogenicity, and safety carried out with the existing overall clinical dataset, updated with new available data since MAA. Data in the new target population (6 to 8 years) were presented along with an outline of the data in subjects 9 to 17 years and 2 to 5 years (as benchmark and to update results from the prior submission). The efficacy and immunogenicity data focus on subjects dengue-immune at baseline, in line with current labelling recommendations. General safety data are presented irrespective of serostatus, and in dengue immune subjects.

The integrated analyses of efficacy include data from two Phase 3 efficacy trials and one Phase 2b PoC trial. The Phase 3 pivotal efficacy trials were CYD14 (children 2 to 14 years in AP countries) and CYD15 (children 9 to 16 years in LatAm). The Phase 2b PoC study CYD23/CYD57 was performed in Thailand in subjects aged 4 to 11 years. Since MAA, the data were updated with the final results of the 2 pivotal efficacy studies for which data of 5 years follow-up after the last dose are now available. Efficacy data in the new target population of the claimed indication (children 6 to 8 years) and in children 2-5 years are mainly from CYD14 (and limited data from CYD23), while data in children 9-16 years are both from CYD14 and CYD15 (and limited data from CYD23). Analyses are limited to subjects for whom baseline serostatus data are available. For the Immunogenicity Subset analyses (FASI, pooled over studies), there were 236 and 126 seropositive subjects 6-8 years respectively in the CYD and Control Groups. There were 1619 and 784 children 9-16 years, and 259 and 115 children 2 to 5 years, in respective groups. Approximately 70% of the subjects in the Immunogenicity Subset are dengue seropositive at baseline. The NS1 Supplemental Analyses are presented in support, as this allowed an assessment on a larger number of cases. The sub-cohort of the NS1 case-cohort study included a random selection of 10% of the entire study cohorts. This represented 3578 subjects irrespective of serostatus and age (CYD14, n=1099; CYD15, n=2130; CYD23/57, n=349). Of these 3578 subjects, 374 were 6-8 years. All relevant cases were also included in the case-cohort analyses. The proportion of subjects classified as seropositive varied across the methods (62.4%-78.3%).

The integrated immunogenicity analysis included results of 12 studies, i.e. two large-scale pivotal efficacy studies CYD14 and CYD15, and 10 supportive studies CYD13, CYD22, CYD24, CYD28, CYD30, CYD65 (Phase 2 studies), CYD23 (Phase 2b), CYD32 (Phase 3) and CYD71 and CYD67 (Phase 3b, co-administration studies). All 12 clinical trials were conducted in healthy subjects (2-50 yoa) in endemic regions (Asia Pacific and Latin America and the Caribbean) and are consistent in terms of the general study design, vaccine formulation and schedule. Although twelve studies were included in the integrated immunogenicity analysis, only 6 of them included children from 2-8 years. Children 6-8 years are nearly exclusively from AP countries (as are children from 2-5 years), while children 9-17 are from both regions, although mainly from LatAm. Because of the low number of seropositive subjects included in all the studies, with the exception of study CYD14, the assessment was mainly focused on the results obtained in the CYD14 study, that included 168 6-8 years vaccinated children.

The pooled/integrated safety analysis includes 22 clinical studies used for the evaluation of the CYD dengue vaccine final formulation, in subjects aged ≥ 6 years irrespective of the vaccination schedule ("all studies"): 3 Phase I (CYD04, CYD05, and CYD06), 2 Phase IIa (CYD10 and CYD11), 9 Phase II (CYD12, CYD13, CYD22, CYD24, CYD28, CYD30, CYD47, CYD51, and CYD65 [intermediate results – until approximately one year after the primary series]), 2 Phase IIb (CYD23/57), 4 Phase III (CYD14, CYD15, CYD17, and CYD32) and 2 Phase IIIb (CYD71 and CYD67). Data from 17 of these studies using the final formulation and a 3-dose vaccination schedule at Day 0, Month 6 and Month 12 (D0/M6/M12) in subjects ≥ 6 years, are referred to in the text as the "Main Studies" (CYD12, CYD13, CYD14, CYD15, CYD17, CYD22, CYD24, CYD28, CYD30, CYD32, CYD47, CYD51, CYD65, CYD67, CYD71, CYD23/57). The safety profile of the CYD dengue vaccine in subjects aged 6 to 8 years according to the 3-dose schedule was evaluated based on pooled data of 6 studies (CYD14, CYD22, CYD23/CYD57, CYD24, CYD28, and CYD32). A total of 3233 and 768 individuals aged 6 to 8 years regardless of the baseline dengue serostatus were considered for general safety and reactogenicity, respectively. Among subjects from the combined regions with an available dengue serostatus (529 out of 3233 subjects), 294 were baseline seropositive (55.6%).

3.2. Favourable effects

Efficacy was assessed post hoc in seropositive subjects from the Immunogenicity Subset and in the supportive NS1 Supplemental analyses from the pivotal CYD14 and CYD15 trials. Vaccine efficacy was demonstrated up to the first year post-dose 3 in the population 6-16 years living in high endemic countries.

Up to the first year post-dose 3, efficacy against virologically confirmed dengue (VCD) was demonstrated in the new target population (6-8 years). There is a trend towards lower efficacy in this age group (approximately 70%) compared to the 9-16 years (approximately 80%). Results in the Immunogenicity Subset are overall supported by those of the NS1 Supplemental Analyses, and are consistent across methods and studies. Overall, in the population 6-16 years, VE was 79.9 % (95% CI: 66.9; 87.7) (Immunogenicity Subset, FASI, pooled analysis of CYD14 + CYD15+ CYD23).

Data up to the first year post-dose 3 also suggest efficacy against hospitalised VCD in both age categories. For severe VCD, the number of cases is too limited to reliably estimate efficacy by age, but those numbers are in favour of Dengvaxia. Efficacy points estimates were higher compared to those of efficacy against VCD. Hospitalised VCD (HVCD) and severe VCD (SVCD) efficacies tended to decrease with decreasing age. In children 6-16 years (NS1 Supplemental analyses, pooled analysis CYD14+CYD15), efficacy against HVCD ranged between 90.3% (95% CI: 80.1; 95.3) and 95.7% (95% CI: 87.9; 98.5), while efficacy against SVCD ranged between 91.8% (95% CI: 72.3; 97.6) and 96.8% (95% CI: 75.9; 99.6).

The long-term data (up to Year 6) indicate a decrease of efficacy over time after Year 2 (i.e. 1 year post-dose 3).

VCD efficacy (Active Phase) against serotype 2, and to a lesser extent against serotype 1, tends to be lower compared to other serotypes. In contrast to efficacy, GMTs tend to be consistently lower for serotype 4 when compared to serotypes 1-3 GMTs.

The limited immunogenicity data of the main study CYD14 indicate that higher post-dose 3 neutralizing antibody titers were observed in the 9-17 years age group when compared to 6-8 years age group. GMTs observed at Year 5 were also lower in the 6-8 years when compared to the 9-17 years age groups.

A trend for a decrease in dengue-neutralizing antibody GMTs against all 4 serotypes from post-dose 3 through Year 5 was observed. GMTs for each serotype remained at higher levels than those observed at baseline in all age categories.

3.3. Uncertainties and limitations about favourable effects

Uncertainties remain with respect to the actual level of efficacy in seropositive individuals, in the various age categories. All efficacy analyses are post-hoc. The pivotal trials were not designed to assess efficacy according to dengue immune serostatus at baseline (the Immunogenicity Subset represents 10% of the population initially enrolled in the efficacy studies). To address this limitation, the MAH performed the post-hoc NS1 Supplemental Analyses. Nevertheless, the power of the analyses remains limited. Estimates in the 6-8 years are imprecise, for efficacy against VCD but even more for efficacy against less frequent endpoints such as HVCD and SVCD. In addition, there are limitations of the NS1 approaches to classify baseline serostatus (as the real false positive rate is unknown and biases related to differential misclassification are possible). It is nevertheless reassuring that efficacy results in the Immunogenicity Subset are in general supported by the NS1 Supplemental analyses (and consistent across methods).

Efficacy data were generated in highly endemic populations (LatAm and Asia Pacific regions). The data for the 6-8 years children were generated in the Asia Pacific regions. There is no efficacy data in EU endemic territories. It is unclear to which extend the level of efficacy can be extrapolated to different epidemiological contexts such as areas of low endemicity and to EU travellers who have been previously infected with dengue. The level of efficacy is expected to be lower in areas of lower endemicity. The pre-existing dengue immune status (magnitude and quality) and other aspects of the epidemiological context (such as pre-existing immunity related to the various serotype circulation, prior infection and/or vaccination against other flaviviruses) may influence efficacy. It was observed that lower baseline immunity is associated with lower immunogenicity.

Efficacy persistence (VCD, HVCD, SVCD) was not demonstrated for the 6-16 years children living in endemic areas in the CYD14 and CYD15. Efficacy decreases over time starting from 1 year post-dose 3 (i.e. after the Active Phase). Data are limited (only HVCD for Year 3 and Year 4) and estimates are very imprecise from Year 3 to Year 6. Overall, considering CYD14 and CYD15 together, persistence of protection appears to be low or absent after the Active Phase. At Year 5-6, efficacy is lacking/poorly sustained. Results are inconsistent between the Immunogenicity Subset (lack of efficacy persistence) and the NS1 analyses (some level of efficacy still seen during the SEP (Years 5-6).

Levels of specific nAb were shown to decrease over time. It is not known if the nAb titers will continue to decrease after more than 5 years post-third vaccination.

Results of VE against VCD due to each serotype during the SEP tended to vary across studies (NS1 Supplemental Analyses). In CYD14, some persisting efficacy was observed for all serotypes. In CYD15, there is a lack of efficacy persistence for serotypes 1, 2 and 3, while efficacy against VCD is observed for serotype 4 during the SEP. Results are difficult to interpret due to small numbers, limitations of the

post-hoc NS1 analyses, and the possible impact of the Zika outbreak that occurred in Latin America during the SEP.

Protective immune responses and efficacy persistence could be affected by the wild type virus circulation (which can vary over year) and by the co-circulation of other flaviviruses. Influence on immune responses and efficacy could vary according to serotype.

Uncertainties on persistence of immunity and efficacy is even greater for people living in low endemicity areas and for EU travellers who have been previously infected with dengue but live outside endemic areas. Persistence of efficacy cannot be extrapolated from highly endemic areas where pre-existing immunity is higher and regular natural boosting of immunity occur, which may contribute to maintain efficacy over time.

Based on efficacy persistence data, there is a need for booster doses. Three studies (CYD63, CYD64, CYD65) investigated a booster dose at 1, 2, 4 or 5 years after the last injection of the 3-dose schedule in subjects 9-50 years living in Asian and LatAm endemic areas. No or modest transient increase of neutralizing Ab titers was observed after the boost. The booster effect was variable across serotypes and studies. Why there is a lack/limited booster effect with Dengvaxia remains not understood in terms of mechanisms and clinical implications. The added value of and appropriate timing for booster doses remains to be elucidated according to the various epidemiological contexts and for travellers.

Overall, vaccine efficacy against VCD, HVCD, and SVCD tends to be lower with lowering age. The reasons are not fully understood. The independent effect of age, study region (local epidemiology), misclassification of serostatus (higher false positive rate in the youngest), and baseline immunity (magnitude and quality) on the results, is difficult to disentangle.

VE data are available for subjects 6-16 years of age. No efficacy data are available over 16 years.

Analyses by serotype and age categories are statistically not meaningful (estimates were too imprecise).

Only healthy subjects were included in the efficacy studies. No efficacy data are available in children with comorbidities, or in immunocompromised children (individuals presenting with congenital or acquired immunodeficiency, receiving immunosuppressive therapy).

There is no established immunological correlate of protection. The clinical relevance of the immunogenicity results is unknown.

There is no data yet on co-administration with other vaccines.

3.4. Unfavourable effects

In subjects aged 6 to 8 years regardless of the baseline dengue serostatus, the safety profile of the CYD dengue vaccine and Placebo or Control were overall similar, as most of the various safety parameters were reported with similar frequencies in the 3 groups. However, a trend toward a slightly higher incidence of solicited systemic reactions in the CYD dengue vaccine Group was observed.

Most solicited reactions were Grade 1, occurred within 3 days after injection, and were of short duration. The incidence of solicited systemic reactions tended to decrease with subsequent injections while the incidence of each solicited injection site reactions remained stable after each injection. Unsolicited AEs reported during the 28-day monitoring period after each injection were common medical conditions normally observed in this age group and occurred with similar frequency compared to Placebo or Control Groups. Few of them were considered related to the CYD dengue vaccine. All SAEs reported, except one (a case of acute disseminated encephalomyelitis), were considered as unrelated to vaccination, and were also similar in nature to that observed in the Placebo and Control Groups. There was no cluster of events

in the 28-day period post-injection. No death was reported after CYD dengue vaccine administration in subjects aged 6 to 8 years. No viscerotropic events were reported in any study. No severe immediate anaphylactic reactions have been reported. 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 (up to 5 years after the last injection).

Solicited injection site reactions, solicited systemic reactions and unsolicited non-serious AE (mainly systemic) were observed at a lower frequencies in dengue seropositive subjects compared to all subjects regardless of baseline dengue serostatus.

In the RMP, the important identified risks remain: allergic reactions (including anaphylactic reactions), and increased risk of severe and/or hospitalized dengue following vaccination in individuals not previously infected by dengue virus who are inadvertently vaccinated with Dengvaxia.

3.5. Uncertainties and limitations about unfavourable effects

The majority of the vaccinated children aged 6 to 8 years (3179 children of the 3233) were from endemic Asia Pacific (AP), and all the subjects who provided ethnicity data were Asian (i.e. no ethnic origin data collected for the 54 children in the LatAm region). Therefore, the representability of the included population is questioned, in particular concerning the extrapolation of one epidemiological context to another in the context of the theoretical risk of cross-enhancement of other flaviviruses.

Moreover, it is noteworthy that the safety database is limited for the dengue baseline positive children aged 6 to 8 years: 294 were baseline seropositive among those with an available dengue serostatus (529 out of 3233 subjects).

As identified in the RMP, the important potential risks are the vaccine-associated viscerotropic disease, the vaccine-associated neurotropic disease, and the risk of severe dengue disease due to waning protection against dengue disease over time. And the missing information are the safety in immunocompromised subjects (including subjects with congenital or acquired immune deficiency, or with Human Immunodeficiency Virus (HIV) infection with impaired immune function) and co-administration of CYD dengue.

The use of the vaccine in subjects who did not yet acquire a natural immunity against dengue virus (seronegatives) was associated with an identified risk for severe dengue, which can be potentially fatal. Therefore, the laboratory approaches and tests that will be used to confirm prior dengue exposure before vaccination are of importance. Those approaches are included in local PH recommendations and clinical guidelines.

3.6. Effects Table

Effects Table for the extension of indication for Dengvaxia to: prevention of dengue disease caused by dengue virus serotypes 1, 2, 3 and 4 in individuals 6 to 8 years of age with prior dengue virus infection and living in endemic areas CYD dengue vaccine (data cut-off: 19/03/2020):

Effect	Short description	Vaccine efficacy	(95% CI)	Uncertainties / Strength of evidence	References
	Favourable Effects				
Efficacy against VCD any serotype, M0-M25	6-8 years	71.6%	28.9; 88.7	Posthoc analyses	Pooled analyses, Immunogenicity subset
	9-16 years	81.9%	67.2; 90.0	Posthoc analyses	Pooled analyses, Immunogenicity subset
Efficacy against VCD any serotype, Year 5-6	6-8 years	42.8%	-85.4; 81.9	Posthoc analyses	Pooled analyses, Immunogenicity subset
	9-16 years	-22.4%	-247.6; 56.9	Posthoc analyses	Pooled analyses,

Effect	Short description	Vaccine efficacy	(95% CI)	Uncertainties / Strength of evidence	References
					Immunogenicity subset
Efficacy against HVCD any serotype, M0-M25	6-8 years	1 and 5 cases in CYD vs Placebo Groups		Posthoc analyses	Pooled analyses, Immunogenicity subset
	9-16 years	0 and 6 cases in CYD vs Placebo Groups		Posthoc analyses	Pooled analyses, Immunogenicity subset
	6-8 years	83.9 % to 89.4%	(-56.7; 98.3) to (8.2; 98.8)	Posthoc analyses	NS1 Supplemental Analyses (pooled)
	9-16 years	91.0% to 96.4%	(79.7; 96.0) to (88.2; 98.9)	Posthoc analyses	NS1 Supplemental Analyses (pooled)
Efficacy against HVCD any serotype, Year 5-6	6-8 years	3 and 4 cases in CYD vs Placebo Groups		Posthoc analyses	Pooled analyses, Immunogenicity subset
	9-16 years	3 and 2 cases in CYD vs Placebo Groups		Posthoc analyses	Pooled analyses, Immunogenicity subset
	6-8 years	60.8% to 87.4%	(-10.9; 86.2) to (44.0; 97.2)	Posthoc analyses	NS1 Supplemental Analyses (pooled)
	9-16 years	47.4% to 70.9%	(-15.4; 76.0) to (24.2; 88.9)	Posthoc analyses	NS1 Supplemental Analyses (pooled)
Efficacy against SVCD any serotype, M0-M25	6-8 years	0 and 1 cases in CYD vs Placebo Groups		Posthoc analyses	Pooled analyses, Immunogenicity subset
	9-16 years	0 and 2 cases in CYD vs Placebo Groups		Posthoc analyses	Pooled analyses, Immunogenicity subset
	6-8 years	46.2% and 80.0% (not computed for all methods), not conclusive		Posthoc analyses	NS1 Supplemental Analyses (pooled)
	9-16 years	Number of cases too limited		Posthoc analyses	NS1 Supplemental Analyses (pooled)
Efficacy against SVCD any serotype, Year 5-6	6-8 years	The number of subjects with a SVCD was very low and precluded the calculation of VE. The data do not suggest an increased risk associated with vaccination, for both the subcategories 6-8 years and 9-16 years		Posthoc analyses	Pooled analyses, Immunogenicity subset
	9-16 years			Posthoc analyses	Pooled analyses, Immunogenicity subset
	6-8 years			Posthoc analyses	NS1 Supplemental Analyses (pooled)
	9-16 years			Posthoc analyses	NS1 Supplemental Analyses (pooled)

Effect	Short description	Unit	Treatment	(95% CI)	Placebo	(95% CI)	Control	(95% CI)	References
Unfavourable Effects									
Immediate unsolicited AE			0	(0.0; 0.5)	0	(0.0; 1.3)	0	(0.0; 0.1)	
Solicited injection site reaction			56.1	(52.5; 59.7)	54.3	(48.3; 60.3)	55.9	(50.7; 61.1)	
	Pain		51.4	(47.8; 55.0)	48.9	(42.9; 55.0)	51.4	(46.1; 56.6)	
	erythema		21.7	(18.8; 24.8)	24.1	(19.2; 29.6)	22.7	(18.5; 27.3)	
	swelling		16.2	(13.7; 19.0)	16.5	(12.4; 21.4)	16.5	(12.9; 20.7)	
Solicited systemic reaction			67.5	(64.0; 70.8)	60.8	(54.8; 66.6)	59.5	(54.3; 64.5)	
	Fever		19.6	(16.8; 22.6)	18.7	(14.3; 23.8)	15.7	(12.1; 19.8)	
	Headache		51.5	(47.9; 55.1)	48.9	(42.9; 55.0)	47.8	(42.6; 53.1)	
	Malaise		44.2	(40.6; 47.8)	39.2	(33.4; 45.2)	38.6	(33.7; 43.8)	
	Myalgia		40.1	(36.6; 43.7)	34.5	(29.0; 40.4)	34.6	(29.8; 39.7)	
	asthenia		32.8	(29.5; 36.3)	32.4	(26.9; 38.2)	29.2	(24.6; 34.1)	
Unsolicited non-serious AE			43.8	(40.2; 47.3)	44.2	(38.3; 50.3)	45.7	(40.5; 50.9)	
Unsolicited non-serious AR			3.1	(2.0; 4.6)	1.8	(0.6; 4.1)	1.6	(0.6; 3.5)	
	Injection site haemorrhage		0.4	(0.1; 1.1)	0	(0.0; 1.3)	0	(0.0; 1.0)	SafAS Main studies pooled
	Injection site induration		0.4	(0.1; 1.1)	0.4	(0.0; 2.0)	0.3	(0.0; 1.5)	
	Injection site bruising		0.3	(0.0; 0.9)	0	(0.0; 1.3)	0	(0.0; 1.0)	
	Vomiting		0.9	(0.4; 1.9)	0	(0.0; 1.3)	0.3	(0.0; 1.5)	
	Decreased appetite		0.4	(0.1; 1.1)	0	(0.0; 1.3)	0	(0.0; 1.0)	
Unsolicited non-serious injection site AR			1.6	(0.8; 2.7)	1.1	(0.2; 3.1)	0.8	(0.2; 0.4)	
Unsolicited non-serious systemic AE			43.5	(39.9; 47.1)	44.2	(38.3; 50.3)	45.7	(40.5; 50.9)	
Unsolicited non-serious systemic AR			1.8	(1.0; 3.0)	0.7	(0.1; 2.6)	0.8	(0.2; 2.4)	
Anaphylactic reaction (SMQ)			0	(0.0; 0.5)	0	(0.0; 1.3)	0	(0.0; 1.0)	
Non-serious allergic reaction (targeted list)			0.8	(0.3; 1.7)	0.4	(0.0; 2.0)	0.3	(0.0; 1.5)	
Post-vaccination dengue-like syndrome			0	(0.0; 0.5)	0	(0.0; 1.3)	0	(0.0; 1.0)	
Discontinuation due to AE			0.2	(0.11; 0.49)	0.8	(0.41; 1.39)	0.8	(0.39; 1.31)	
SAE ≤ 28 days			1.3	(0.91; 1.72)	1.9	(1.24; 2.68)	1.8	(1.22; 2.60)	
SAE > 28 days to 6 months post dose			5.6	(4.83; 6.45)	7.0	(5.74; 8.38)	6.9	(5.69; 8.24)	
Neurological disorder SAE ≤ 30 days			<0.1	(0.00; 0.17)	0.2	(0.04; 0.58)	0.2	(0.04; 0.55)	
Neurological disorder SAE > 30 days to 6 months post dose			0.1	(0.03; 0.32)	0.3	(0.07; 0.68)	0.3	(0.07; 0.64)	
Death within 6 months			0	(0.00; 0.11)	0.3	(0.11; 0.77)	0.3	(0.10; 0.73)	

Abbreviations: virologically-confirmed dengue; HVCD: Hospitalized VCD: SVCD: Severe VCD; SafAS: Safety Analysis set

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Efficacy over the first two years was demonstrated against VCD in in the new target population of children aged 6 to 8 years. Data also suggest efficacy against hospitalised VCD and against severe VCD. Overall, vaccine efficacy against VCD, HVCD, and SVCD tends to be lower in the 6 to 8 years age group compared to the 9-16 years. VCD VE against serotype 2, and to a lesser extent against serotype 1, is lower compared to the other serotypes. Efficacy decreases over time after 1 year post-dose 3, whether some level of efficacy is maintained up to Year 6 post-vaccination is not clear (in the 6-8 years and in the 9-16 years children).

Overall, the safety profile of the CYD dengue vaccine in children aged 6 to 8 years was not different than the one in children aged 9 to 17 years, which are part of the population in which the vaccine was initially authorised.

3.7.2. Balance of benefits and risks

Altogether, the benefit of Dengvaxia outweighs the unfavourable effects linked mainly to reactogenicity. The balance of benefits and risks in the new target population of 6-8 years is considered overall similar to that of older children.

3.8. Conclusions

The overall B/R of Dengvaxia is positive.

The extension of indication can be recommended for approval.

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indications to include paediatric population from 6 years of age for Dengvaxia; as a consequence, sections 4.1, 4.2, 4.8 and 5.1 of the SmPC and sections 1, 2 and 4 of the Package Leaflet are updated. Furthermore, the MAH took the opportunity to add instructions for the installation of the needle in the SmPC and the Package Leaflet of the single-dose presentation.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB are recommended.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP EMEA-001545-PIP01-13-M02 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.