1 NAME OF THE MEDICINAL PRODUCT

Dengvaxia, powder and solvent for suspension for injection.
Dengue tetravalent vaccine (live, attenuated).

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

After reconstitution, one dose (0.5 mL) contains:

CYD dengue virus serotype 1*.....4.5 - 6.0 log_{10} $CCID_{50}$/dose**
CYD dengue virus serotype 2*.....4.5 - 6.0 log_{10} $CCID_{50}$/dose**
CYD dengue virus serotype 3*.....4.5 - 6.0 log_{10} $CCID_{50}$/dose**
CYD dengue virus serotype 4*.....4.5 - 6.0 log_{10} $CCID_{50}$/dose**
* Produced in serum-free Vero cells by recombinant DNA technology
** $CCID_{50}$: 50% Cell Culture Infectious Dose.

Excipients with known effect: (see Section 4.4)
Phenylalanine……41 micrograms
Sorbitol…….…….9.38 milligrams

For a full list of excipients, see Section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for suspension for injection.

Prior to reconstitution, the vaccine is a white, homogenous, freeze-dried powder with possible retraction at the base(ring-shaped cake possible).

The solvent is a clear and colorless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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 test-confirmed previous dengue infection (see sections 4.2, 4.4 and 4.8).

The use of Dengvaxia should be in accordance with official recommendations including national recommendation.

4.2 Posology and method of administration

Screening

Dengvaxia should only be administered to individuals with a previous dengue infection. Previous dengue infection must be confirmed by a test, either documented in the medical history or performed prior to vaccination.
In non-endemic areas or low transmission settings, the lower the proportion of true seropositive individuals, the higher the risk of false seropositives with any test used to determine dengue serostatus. Thus, testing performed prior to vaccination should be limited to individuals who have been in potential contact with dengue virus (e.g. individuals who lived before or had recurrent stay in endemic

areas) and who are likely to be exposed to dengue in the future. The objective is to minimize the risk of a false positive test, as in non-endemic areas, the proportion of individuals truly infected by dengue is considered generally very low.

Posology

Children 6 to 8 years of age

The vaccination schedule consists of 3 injections of one reconstituted dose (0.5 mL) to be administered at 6-month intervals.
Children and adults 9 to 45 years of age

The vaccination schedule consists of 2 injections of one reconstituted dose (0.5 mL) to be administered at 6-month intervals.

Other paediatric population

Dengvaxia should not be used in children less than 6 years of age (see sections 4.8). Available data do not support the safety and efficacy in individuals younger than 6 years (see section 5.1, subsection 2.4).

Method of administration

Immunisation should be carried out by subcutaneous (SC) injection preferably in the upper arm in the region of deltoid.

Do not administer by intravascular injection.

For instructions on reconstitution of Dengvaxia before administration, see Section 6.6.

4.3 Contraindications

- Hypersensitivity to the active substance, to any of the excipients listed in section 6.1, or after prior administration of Dengvaxia or a vaccine containing the same components.
- Individuals with congenital or acquired cell-mediated immune deficiency, including immunosuppressive therapies such as chemotherapy or high doses of systemic corticosteroids (e.g. 20mg or 2mg/kg of prednisone for 2 weeks or more) within 4 weeks prior to vaccination.
- Individuals with symptomatic HIV infection or with asymptomatic HIV infection when accompanied by evidence of impaired immune function.
- Pregnant women (see section 4.6).
- Breast-feeding women (see section 4.6).

4.4 Special warnings and precautions for use

Protection

A protective immune response with Dengvaxia may not be elicited in all vaccinees. It is recommended to continue personal protection measures against mosquito bites after vaccination.

Special patient groups

Individuals who have not been previously infected by dengue virus or for whom this information is unknown

Individuals who have not been previously infected by dengue virus should not be vaccinated because an increased risk of hospitalisation for dengue and clinically severe dengue (predominantly grade 1 or 2 Dengue Hemorrhagic Fever) has been observed in not previously infected, vaccinated individuals during the long-term follow-up of clinical trials (see section 4.8).

In the absence of documented prior dengue virus infection, previous infection must be confirmed by a test before vaccination (see section 4.2). To avoid vaccination of false positives, only test methods with adequate performance in terms of specificity and cross-reactivity based on the local disease epidemiology should be used.

Travellers

Vaccination is not recommended for individuals living in non-endemic areas, who have not been in potential contact with dengue virus and who only occasionally travel to endemic areas.
Others

Administration of Dengvaxia must be postponed in individuals suffering from moderate to severe febrile or acute disease.

Vaccination should be preceded by a review of the individual's medical history (in particular, previous vaccinations and possible adverse reactions which occurred after vaccination).

Appropriate medical treatment and supervision must always be readily available in the event of an anaphylactic reaction following administration of the vaccine.

Syncope (fainting) can occur following, or even before, any vaccination as a psychogenic response to injection with a needle. Procedures should be in place to prevent injury from falling and to manage syncopal reactions.

The tip caps of the prefilled syringes contain a natural rubber latex derivative, which may cause allergic reactions in latex sensitive individuals.

Women of childbearing potential have to use effective contraception during at least one month after each dose (see section 4.6).

Dengvaxia must not be administered by intravascular injection under any circumstances.

Dengvaxia contains phenylalanine, sodium and sorbitol

Dengvaxia contains 41 micrograms of phenylalanine in each 0.5 ml dose. Phenylalanine may be harmful for people with phenylketonuria (PKU), a rare genetic disorder in which phenylalanine builds up because the body cannot remove it properly.

Dengvaxia contains less than 1mmol of sodium (23 mg) per 0.5 ml dose, that is to say essentially “sodium-free”.

Dengvaxia contains 9.38 milligrams of sorbitol in each 0.5 ml dose.

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

4.5 Interaction with other medicinal products and other forms of interaction

For patients receiving treatment with immunoglobulins or blood products containing immunoglobulins, such as blood or plasma, it is recommended to wait for at least 6 weeks, and preferably for 3 months, following the end of treatment before administering Dengvaxia, in order to avoid neutralization of the attenuated viruses contained in the vaccine.

Dengvaxia should not be administered to subjects receiving immunosuppressive therapies such as chemotherapy or high doses of systemic corticosteroids within 4 weeks prior to vaccination (see section 4.3).

Use with other vaccines

Dengvaxia has been evaluated in one clinical study on concomitant administration with Tdap (Tetanus Toxoid, Reduced Diphtheria Toxoid and Acellular Pertussis Vaccine, Adsorbed) (688 subjects, 9 to 60 years of age), and in two clinical studies with two HPV vaccines (Human Papillomavirus Vaccine, Recombinant) (528 subjects, 9 to 13 years of age and 480 subjects, 9 to 14 years of age).

There was no evidence of an increased rate of reactogenicity or change in the safety profile of the vaccines when Tdap and HPV vaccines were administered concomitantly with Dengvaxia in any of these studies. Antibody responses to Dengvaxia and the Tdap vaccine or HPV vaccine components were not negatively affected by concomitant administration.

4.6 Fertility, pregnancy and lactation

Pregnancy

Animal studies did not indicate any direct or indirect harmful effects with respect to reproductive toxicity (see Section 5.3).

There is limited amount of data from the use of Dengvaxia in pregnant women. These data are not sufficient to conclude on the absence of potential effects of Dengvaxia on pregnancy, embryo-foetal development, parturition and post-natal development.

Dengvaxia is a live attenuated vaccine, therefore Dengvaxia is contraindicated during pregnancy (see section 4.3).

Women of childbearing potential have to use effective contraception during at least one month after each dose.

Breastfeeding

Animal studies did not indicate any direct or indirect harmful effects with respect to lactation.
There is very limited experience on dengue virus excretion via breast milk.
Also, considering that Dengvaxia is a live attenuated vaccine and that there is very limited experience from post marketing data with Dengvaxia in lactating women, the vaccine is contraindicated during lactation (see section 4.3).

Fertility

No specific studies have been performed on fertility.
Animal studies did not indicate any harmful effects with respect to female fertility (see Section 5.3).

4.7 Effects on ability to drive and use machines

Dengvaxia has minor influence on the ability to drive and use machines.

4.8 Undesirable effects

a. Summary of the safety profile

In subjects 6 to 45 years of age, the most frequently reported reactions whatever the dengue serostatus prior to vaccination, were headache (51%), injection site pain (49%), malaise (41%), myalgia (41%), asthenia (32%), and fever (14%).

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 doses of Dengvaxia as compared to the first dose.

Allergic including anaphylactic reactions have been reported very rarely.

Overall, the same adverse reactions but at lower frequencies were observed in dengue seropositive subjects. Also, the same adverse reactions but at lower frequencies were observed in the 2-dose schedule compared to the 3-dose schedule.

b. Tabulated list of adverse reactions

Adverse reactions are listed according to the following frequency categories:
Very common: ≥ 1/10
Common: ≥ 1/100 to < 1/10
Uncommon: ≥ 1/1000 to < 1/100
Rare: ≥ 1/10,000 to < 1/1000
Very rare: (<1/10 000)

Adverse reactions collected within 28 days after any dose during clinical studies from 6 to 45 years of age, on a reactogenicity subset of 1492 adults and 4434 children, and adverse reactions observed during commercial use are presented in Table 1 for children 6 to 17 years old and in Table 2 for adults 18 to 45 years old.

Table 1: Adverse Reactions from Clinical Studies and reported during commercial use in children (6 to 17 years old)

System Organ Class	Frequency	Adverse Events
Infections and infestations	Uncommon	Upper respiratory tract infection
	Rare	Nasopharyngitis
Immune system disorders	Very rare	Allergic including anaphylactic reactions*
Nervous system disorders	Very common	Headache
	Rare	Dizziness
Respiratory, thoracic and mediastinal disorders	Rare	Rhinorrhoea Cough Oropharyngeal pain
Gastrointestinal disorders	Uncommon	Vomiting
	Rare	Nausea
Skin and subcutaneous tissue disorders	Rare	Rash Urticaria
Musculoskeletal and connective tissue disorders	Very common	Myalgia
	Rare	Neck pain
General disorders and administration site conditions	Very common	Malaise Asthenia Fever Injection site reactions (pain, erythema)
	Common	Injection site swelling
	Uncommon	Injection site reactions (, pruritus, induration, haemorrhage, hematoma)
	Rare	Chills

* Adverse reactions from spontaneous reporting.

Table 2: Adverse reactions from Clinical Studies and reported during commercial use in adults (18 to 45 years old)

System Organ Class	Frequency	Adverse Events
Infections and infestations	Uncommon	Upper respiratory tract infection Nasopharyngitis
Blood and lymphatic tissue disorders	Uncommon	Lymphadenopathy
Immune system disorders	Very rare	Allergic including anaphylactic reactions*
Nervous system disorders	Very common	Headache
	Uncommon	Dizziness
Respiratory, thoracic and mediastinal disorders	Uncommon	Oropharyngeal pain Cough
Gastrointestinal disorders	Uncommon	Nausea Vomiting Dry mouth
Skin and subcutaneous tissue disorders	Uncommon	Rash
Musculoskeletal and connective tissue disorders	Very common	Myalgia
	Uncommon	Neck pain Arthralgia
General disorders and administration site conditions	Very common	Injection site pain Malaise Asthenia
	Common	Fever Injection site reactions (erythema, hematoma, swelling, pruritus)
	Uncommon	Injection site reactions (induration, warmth) Fatigue Chills
	Rare	Injection site haemorrhage

* Adverse reactions from spontaneous reporting.

c. Hospitalised and/or clinically severe dengue fever in long-term safety follow-up data

In an exploratory analysis of the long-term follow-up from the first dose in three efficacy studies, an increased risk of hospitalisation for dengue including clinically severe dengue (predominantly Dengue Haemorrhagic Fever grade 1 or 2 [WHO 1997]) has been observed in vaccinees with no previous dengue infection. Over a period of 6 years, in subjects with no previous dengue infection, the risk of severe dengue is increased by 2.31 fold (95% CI: 0.70; 7.66) in subjects 6 to 16 years of age vaccinated with Dengvaxia as compared to non-vaccinated subjects in the same age group. In subjects 6 years of age or older, it was estimated that during a 6 year follow-up about 12 additional hospitalized dengue cases or 3 additional severe dengue cases per 1000 vaccinees with no previous dengue infection could occur following vaccination. Estimates from the long-term analysis suggest the onset of increased risk was mainly during the 3rd year following the first dose.
This increased risk was not observed in individuals who have been previously infected by dengue virus, where it was estimated that 19 hospitalized dengue cases or 5 severe dengue cases could be prevented per 1000 vaccinees with previous dengue infection during 6 years of follow-up from the first dose.

The estimations described above for a 6 year period are derived from data obtained in the pivotal clinical trials in countries with a particular dengue seroprevalence and epidemiological context. These figures may not be extrapolated to other regions with different seroprevalence and epidemiological situations.

d. Paediatric population

Paediatric data in subjects 6 to 17 years of age

In paediatric population, fever and injection site erythema have been observed with a higher frequency (very common) than in adults (common).

Urticaria (rare) was only reported in subjects 6 to 17 years of age (none in adults).

Paediatric data in subjects below 6 years of age, i.e., outside the age indication

The reactogenicity subset in subjects below 6 years of age includes 2192 subjects as follows: 1287 subjects below 2 years of age and 905 subjects between 2 and 5 years of age.

In subjects 2 to 5 years of age, as compared to subjects above 6 years of age, injection site swelling was more frequently reported (frequency: very common), and additional adverse events were reported (frequency: uncommon): rash maculo-papular and decreased appetite.

Available data do not support safety and effectiveness of Dengvaxia in subjects 2 to 5 years of age (see Section 5.1, subsection 2.4).

In subjects below 2 years of age, the most frequently reported adverse reactions following any dose of Dengvaxia were fever, irritability, appetite lost, abnormal crying and injection site tenderness.

4.9 Overdose

No cases of overdose have been reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Vaccines, Viral vaccines, ATC code: J07BX

1. Mechanism of action

Dengvaxia contains live attenuated viruses. Following administration, the viruses replicate locally and elicit neutralizing antibodies and cell-mediated immune responses against the four dengue virus serotypes (see detailed data below, subsection 3).

2. Clinical efficacy

The clinical efficacy of Dengvaxia was assessed in 3 studies: one supportive Phase IIb efficacy study (CYD23) in Thailand, and 2 pivotal large-scale Phase III efficacy studies, CYD14 in Asia (Indonesia, Malaysia, the Philippines, Thailand, Vietnam) and CYD15 in Latin America (Brazil, Colombia, Honduras, Mexico, Puerto Rico).

The Control Group in dengue studies was defined as subjects who received at least one injection of placebo or comparator vaccine.

In the Phase IIb study, a total of 4002 subjects aged 4 to 11 years were randomised to receive Dengvaxia or a control, regardless of previous dengue infection. Efficacy in subjects 6 to 11 years of age was assessed in 3285 subjects (2184 in vaccine group and 1101 in Control Group).

In the two pivotal Phase III studies (CYD14 and CYD15), a total of approximately 31000 subjects aged 2 to 16 years were randomised to receive either Dengvaxia or placebo, regardless of previous dengue infection. Efficacy in subjects 6 years of age and older was assessed in 19 107 subjects who received Dengvaxia (5193 subjects in CYD14 and 13914 in CYD15) and 9538 subjects who received placebo (2598 in CYD14 and 6940 in CYD15).

At the start of the CYD14 and CYD15 trials, dengue seroprevalence for the overall population at the trial sites ranged from 52.8%-81.1% in CYD14 (Asia-Pacific) and 55.7%-92.7% in CYD15 (Latin America).

The efficacy was assessed during an Active Phase of 25 months, in which surveillance was designed to maximize the detection of all symptomatic virologically-confirmed dengue (VCD) cases regardless of the severity. The active detection of symptomatic dengue cases started on the day of the first dose and lasted until each subject had been followed for at least 13 months after the third dose. This phase includes therefore the primary endpoint observation period from 28 days after the third dose up to the end of the Active Phase.

For the primary endpoint, the incidence of symptomatic VCD cases occurring during the 12-month period from 28 days after the third dose was compared to the Control Group.

Exploratory vaccine efficacy analyses according to dengue serostatus measured by plaque reduction neutralization test (PRNT50) at baseline (before the first dose) were performed in the immunogenicity subset of 2000 subjects each in CYD14 and CYD15 and 300 subjects in CYD23. Of the 2580 subjects 6 to 16 years old in this subset (approximately 80%) who were dengue seropositive at baseline, 1729 subjects received the vaccine (656 subjects in CYD14 and 1073 in CYD15) and 851 subjects received placebo (339 in CYD14 and 512 in CYD15) (see also subsection 3).

2.1 Clinical efficacy data for subjects 6 to 16 years of age in endemic areas, any serostatus at baseline

The Vaccine Efficacy (VE) results according to the primary endpoint (symptomatic VCD cases occurring during the 12-month period starting from 28 days after the third dose) in subjects 6 to 16 years of age (any serostatus at baseline) are shown in Table 3 for studies CYD14, CYD15 and CYD23.

Table 3: VE against symptomatic VCD cases over the 12-month period starting from 28 days after the third dose due to any of the 4 serotypes in subjects 6 to 16 years (any serostatus at baseline).

	CYD14		**CYD15**		**CYD23**		**Pooled CYD14+CYD15**		**Pooled* CYD14+CYD15+ CYD23**	
	Vaccine group	Control group	Vaccine group	Control group	Vaccine group	Control group	Vaccine group	Control group	Vaccine group	Control group
Cases / person-years	67 / 5002	88 / 2479	185 / 12458	236 / 6157	38 / 2146	29 / 1083	252 / 17460	324 / 8636	290 / 19606	353 / 9719
VE % (95%CI)	62.3 (47.6; 73.0)		61.3 (52.8; 68.2)		33.9 (-11.2; 60.3)		61.5 (54.6; 67.4)		59.3 (52.4; 65.1)	

N: number of subjects per study
Cases: number of subjects with at least one symptomatic virologically-confirmed dengue episode in the considered period.
Person-years: sum of time-at-risk (in years) for the subjects during the study period.
CI: confidence interval.
*Pooled results of CYD14, 15 and 23 need to be interpreted cautiously because of differences in the Dengue confirmatory test and acute febrile illness definition between CYD14/15 and CYD23.

In subjects 6 to 16 years of age, the efficacy of Dengvaxia against symptomatic virologically-confirmed dengue (VCD) cases due to any of the 4 serotypes was demonstrated in all three studies, CYD14, CYD15 and CYD23 (see Table 3).

The Vaccine Efficacy (VE) against symptomatic VCD, severe and hospitalised VCD during the 25-month period after the first dose, which were secondary objectives, in subjects 6 to 16 years of age are shown in Table 4 for any serostatus at baseline for studies CYD14, CYD15 and CYD23. For severe VCD cases, two types of endpoints were considered: clinically severe VCD cases and VCD cases that met the 1997 WHO criteria for Dengue Haemorrhagic Fever (DHF).
Vaccine efficacy was demonstrated for these endpoints in CYD14 and CYD15 (see Table 4).

The vaccine efficacy against symptomatic VCD is moderate for serotypes 1 and 2 and higher for serotypes 3 and 4 (see Table 4)

Table 4: VE against symptomatic, Hospitalised or Severe VCD over the 25-month period after the first dose in subjects 6 to 16 years of age (any serostatus at baseline)

	CYD14 VE % (95% CI) N=7791	CYD15 VE % (95% CI) N=20854	Pooled CYD14+CYD15 VE % (95% CI) N=28646	CYD23 VE % (95%CI) N = 3285	Pooled* CYD14+CYD15+ CYD23 VE % (95% CI) N = 31931
Symptomatic VCD					
Any serotype	63.3 (54.9; 70.2)	64.7 (58.7; 69.8)	64.2 (59.6; 68.4)	32.1 (-1.7; 54.4)	62.0 (57.3; 66.2)
Serotype 1	66.5 (52.8; 76.3)	54.8 (40.2; 65.9)	60.0 (50.7; 67.6)	59.0 (9.1; 81.9)	60.0 (51.0; 67.3)
Serotype 2	37.4 (7.8; 57.4)	50.2 (31.8; 63.6)	45.4 (31.1; 56.8)	-4.1 (-87.5; 40.4)	39.1 (24.7; 50.7)
Serotype 3	71.8 (47.1; 85.4)	74.2 (63.9; 81.7)	73.7 (65.0; 80.2)	74.7 (5.7; 94.4)	73.7 (65.3; 80.1)
Serotype 4	78.7 (65.1; 87.4)	80.9 (70.9; 87.7)	80.0 (72.7; 85.3)	89.9 (9.5; 99.8)	80.3 (73.3; 85.5)
Hospitalised VCD†	64.2 (59.6; 68.4)	80.3 (64.7; 89.5)	78.1 (68.3; 84.9)	47.6 (7.6; 70.2)	71.2 (61.2; 78.6)
Clinically severe VCD cases†	60.0 (50.7; 67.6)	95.5 (68.8; 99.9)	88.5 (72.0; 95.3)	49.3 (-598.9; 96.3)	85.7 (68.7; 93.5)
DHF meeting any WHO criteria	45.4 (31.1; 56.8)	95.0 (64.9; 99.9)	88.0 (70.8; 95.1)	49.3 (-598.8; 96.3)	85.2 (67.4; 93.3)

N: number of subjects per study
CI: confidence interval.
VE is calculated using density incidence (cases per 100 person-years at risk)
* Pooled results of CYD14, 15 and 23 need to be interpreted cautiously because of differences in the Dengue confirmatory test and acute febrile illness definition between CYD14/15 and CYD23.
†The efficacy against hospitalised and severe VCD was not a primary objective and cut-off thresholds to define statistical significance were not pre-specified.

2.2 Clinical efficacy data for subjects 6 to 16 years of age in endemic areas, dengue seropositive at baseline

VE against symptomatic VCD cases in subjects 6 to 16 years of age
The Vaccine Efficacy (VE) results according to exploratory analysis of symptomatic VCD cases occurring during the 12-month period starting from 28 days after the third dose in subjects 6 to 16 years of age, seropositives at baseline are shown in Table 5 for the immunogenicity subset of studies CYD14, CYD15 and CYD23.

Table 5: VE against symptomatic VCD cases over the 12-month period starting from 28 days after the third dose due to any of the 4 serotypes in subjects 6 to 16 years (dengue seropositive at baseline).

	CYD14		**CYD15**		**CYD23**		**Pooled CYD14+CYD15**		**Pooled * CYD14+CYD15+ CYD23**	
	Vaccine group	Control group	Vaccine group	Control group	Vaccine group	Control group	Vaccine group	Control group	Vaccine group	Control group
Cases / person-years	6/634	15/325	7/1002	17/472	1/116	3/55	13/1636	32/797	14/1752	35/852
VE % (95%CI)	79.5 (44.2; 93.5)		80.6 (50.7; 93.2)		84.3 (-95.5; 99.7)		80.1 (62.1; 89.6)		80.5 (63.7; 89.5)	

N: number of subjects per study
Cases: number of subjects with at least one symptomatic virologically-confirmed dengue episode in the considered period.
Person-years: sum of time-at-risk (in years) for the subjects during the study period.
CI: confidence interval.
NC: Not computed (the absence of cases in vaccine and control group does not permit to calculate VE nor CI)
*Pooled results of CYD14, 15 and 23 need to be interpreted cautiously because of differences in the Dengue confirmatory test and acute febrile illness definition between CYD14/15 and CYD23.

The Vaccine Efficacy (VE) against symptomatic VCD during the 25-month period after the firstdose, in subjects 6 to 16 years of age who were dengue seropositive at baseline and for the immunogenicity subset for pooled CYD14 + CYD15+CYD23, is estimated at 79.9% (95% CI: 66.9 ; 87.7).

VE against symptomatic VCD cases in subjects 6 to 8 years of age
The vaccine efficacy against symptomatic VCD during the 25-month period after the first dose, in the subgroup of subjects 6 to 8 years of age who were dengue seropositive at baseline (from an exploratory analysis) for CYD14, is estimated at 67.3% (95% CI: 39.9; 82.2).

VE against symptomatic VCD cases 6 months after 2 doses in subjects 9 to 16 years of age
The vaccine efficacy in subjects 9 to 16 years of age, dengue seropositive at baseline (from an exploratory analysis) for CYD14 and CYD15, 6 months post-dose 2 (78.0%; 95% CI: 51.6; 90.0 and 84.2%; 95% CI: 67.3; 92.4 respectively) is similar to that 12 months post-dose 3 (75.2%; 95% CI: 56.0; 86.0 and 75.3%; 95% CI: 64.9; 82.6 respectively).

*VE against hospitalized and severe VCD cases in subjects 6 to 16 years of age*In subjects 6 to 16 years of age, dengue seropositive at baseline (immunogenicity subset), two clinically severe VCD cases in CYD14 and one in CYD15 were reported during the 25-month period after the first injection in the control group versus none in the vaccine group. Eight hospitalized VCD cases in CYD14 were reported in the control group versus one in the vaccine group and two hospitalized VCD cases in CYD15 were reported in the control group versus none in the vaccine group. These data are inconclusive due to the low number of cases in the immunogenicity subset. However, the extrapolated vaccine efficacy (1- Hazard Ratio), obtained from an exploratory analysis (pooled CYD14 + CYD15 +

CYD23) over the 25-month period after the first dose, is estimated at 89.2% (95% CI: 78.5; 94.6) for hospitalized VCD and 95.3% (95% CI: 68.9; 99.3) for severe VCD.

2.3 Clinical efficacy data for subjects 17 to 45 years of age in endemic areas

No clinical efficacy study has been done in subjects from 17 to 45 years from endemic areas. The clinical efficacy of the vaccine is based on bridging of immunogenicity data (see below section 3.3).

2.4 Other paediatric data from efficacy studies in subjects 2 through 5 years of age, i.e., outside the age indication

Efficacy in subjects 2 to 5 years of age was assessed in 712 subjects (482 in vaccine group and 230 in control group) in phase IIb study and in 2481 subjects (1655 subjects in vaccine group and 826 in control group) in the pivotal Phase III study (CYD14). Vaccine efficacy against symptomatic VCD cases over the 12-month period starting from 28 days after the third dose due to any of the 4 serotypes was 43.9% (95% CI: 18.3; 61.4) (pooled CYD14+CYD23). Vaccine Efficacy against symptomatic, severe and hospitalized VCD during the 25-month period after the first dose due to any serotype (pooled CYD14+CYD23), was respectively 35.2% (95% CI: 16.1; 49.9), 30.2% (95% CI: 120.0; 77.8), 35.6% (95% CI: 23.4; 66.4).

2.5 Long-term protection

During a period of 6 years after the first dose, in subjects 6 years of age and above with previous dengue infection, the extrapolated vaccine efficacy [(1-Hazard Ratio)*100] (obtained from an exploratory analysis) is estimated at 75% (95% CI: 64; 83) for hospitalized VCD and 80% (95% CI: 57; 90) for severe VCD.

3. Immunogenicity

During clinical development, immunogenicity data were collected in a total of 7253 subjects 9 months to 60 years of age that received at least one dose of the vaccine.

Among these subjects, a total of 3498 subjects 6 to 45 years of age from endemic areas received at least one dose of Dengvaxia. Most of the subjects were 6 to 17 years of age (n=2836).

During clinical development, neutralizing antibody titres for each serotype were measured with the plaque reduction neutralization test (PRNT) and presented as geometric mean titres (GMTs).
An association between levels of post-dose 2 and post-dose 3 geometric mean titres (GMTs) and the probability of the disease has been demonstrated in efficacy studies.
Higher titres post-dose 2 and post-dose 3 are associated with a lower risk of dengue disease and higher vaccine efficacy, although an immunological correlate of protection has not been established.

In the following Tables the dengue serostatus at baseline (before the first dose), was defined as:

- Dengue seropositivity if the PRNT50 titre ≥ 10 [1/dil] (the lower limit of quantification, LLOQ), against at least one serotype.
- Dengue seronegativity if the PRNT50 titre < the lower limit of quantification against any of the 4 serotypes.

3.1 Immunogenicity data for subjects 6 to 8 years of age in endemic areas

The post-dose 3 GMTs in subjects 6 to 8 years of age in CYD14 are shown in the Table 6.

Table 6: Immunogenicity for dengue seropositive subjects 6 to 8 years of age in CYD14 from endemic areas

		Serotype 1		Serotype 2		Serotype 3		Serotype 4	
Study	**N**	**Pre-dose 1 GMT (95%CI)**	**Post-dose 3 GMT (95%CI)**	**Pre-dose 1 GMT (95%CI)**	**Post-dose 3 GMT (95%CI)**	**Pre-dose 1 GMT (95%CI)**	**Post-dose 3 GMT (95%CI)**	**Pre-dose 1 GMT (95%CI)**	**Post-dose 3 GMT (95%CI)**
CYD14	168	80.8 (57.3; 114)	203 (154; 268)	118 (86.0; 161)	369 (298; 457)	105 (75.5; 145)	316 (244; 411)	48.4 (37.2; 63.0)	175 (145; 211)

N: number of subjects with available antibody titre for the relevant endpoint
Dengue seropositive subjects are subjects with titres above or equal to LLOQ against at least one dengue serotype at baseline
CI: Confidence Interval
CYD14: Indonesia, Malaysia, the Philippines, Thailand, Vietnam.

3.2 Immunogenicity data for subjects 9 to 17 years of age in endemic areas

The post-dose 2 GMTs in subjects 9 to 16 years of age in CYD14 and CYD15 are shown in the Table 7.

Table 7: Immunogenicity for dengue seropositive subjects 9 to 16 years of age in CYD14 and CYD15 from endemic areas

		Serotype 1		Serotype 2		Serotype 3		Serotype 4	
Study	**N**	**Pre-dose 1 GMT (95%CI)**	**Post-dose 2 GMT (95%CI)**	**Pre-dose 1 GMT (95%CI)**	**Post-dose 2 GMT (95%CI)**	**Pre-dose 1 GMT (95%CI)**	**Post-dose 2 GMT (95%CI)**	**Pre-dose 1 GMT (95%CI)**	**Post- dose 2 GMT (95%CI)**
CYD14	485	167 (138; 202)	484(411;570)	319 (274; 373)	935(825;1059)	160 (135; 190)	507(442;581)	83.8 (72.0; 97.6)	317(284;355)
CYD15	1048	278 (247; 313)	912(820;1016)	306 (277; 338)	1050(967;1139)	261 (235; 289)	907(832;989)	73.3 (66.6; 80.7)	353(328;380)

N: number of subjects with available antibody titre for the relevant endpoint
Dengue seropositive subjects are subjects with titres above or equal to LLOQ against at least one dengue serotype at baseline
CI: Confidence Interval
CYD14: Indonesia, Malaysia, the Philippines, Thailand, Vietnam.
CYD15: Brazil, Colombia, Honduras, Mexico, Puerto Rico.

3.3 Immunogenicity data for subjects 18 to 45 years of age in endemic areas

The immunogenicity of the final formulation of the CYD dengue vaccine in adults aged 18 to 45 years in endemic areas was assessed in 3 studies conducted all in Asia-Pacific (CYD22 in Vietnam, CYD28 in Singapore and CYD47 in India).
The GMTs post-dose 2 in subjects 18 to 45 years of age are shown in the Table 8.

Table 8: Immunogenicity for dengue seropositive subjects 18 to 45 years of age from endemic areas

		Serotype 1		Serotype 2		Serotype 3		Serotype 4	
Study	**N**	**Pre-dose 1 GMT (95%CI)**	**Post-dose 2 GMT (95%CI)**	**Pre-dose 1 GMT (95%CI)**	**Post-dose 2 GMT (95%CI)**	**Pre-dose 1 GMT (95%CI)**	**Post-dose 2 GMT (95%CI)**	**Pre-dose 1 GMT (95%CI)**	**Post-dose 2 GMT (95%CI)**
CYD22	19	408 (205; 810)	1031 (497; 2135)	437 (240; 797)	1282 (857; 1920)	192 (117; 313)	558 (394; 792)	86.5 (41.2; 182)	470 (274; 808)
CYD28	66	59.8 (36.8;97.4)	252 (117; 542)	67.1 (40.9; 110)	370 (217; 631)	48.4 (32.9;71.0)	345 (207; 576)	22.1 (14.7;33.4)	326 (204; 521)
CYD47	109	324 (236; 445)	886 (658; 1194)	363 (269; 490)	1055 (837; 1330)	394 (299; 519)	1216 (953; 1551)	80.7 (613; 106)	361(300;436)

N: number of subjects with available antibody titre for the relevant endpoint
Dengue seropositive subjects are subjects with titres above or equal to LLOQ against at least one dengue serotype at baseline
CI: Confidence Interval
CYD28: Low endemic country
CYD22: Vietnam; CYD28: Singapore; CYD47: India;

The bridging of efficacy is based on above available data and overall results. Immunogenicity data available from studies in adults aged 18 to 45 years in endemic regions show that post-dose 2 and post-dose 3 GMTs against each serotype are generally higher in adults than in children and adolescents in CYD14 and CYD15. Therefore, protection is expected in adults in endemics areas although the actual magnitude of efficacy relative to that observed in children and adolescents is unknown.

3.4 Immunogenicity after a 3-dose schedule versus a 2-dose schedule

In a Phase II study (CYD65, conducted in the Philippines and Colombia) in subjects 9 to 50 years of age (n=1050) non-inferiority in the immune response was demonstrated when CYD dengue vaccine was given as a 2-dose schedule compared to CYD dengue vaccine given as a 3-dose schedule, in subjects seropositive at baseline.

The GMTs 28 days after the last dose in subjects 9 to 50 years of age are shown in the Table 9.

Table 9: Immunogenicity after a 3-dose schedule versus a 2-dose schedule for dengue seropositive subjects 9 to 50 years of age from endemic areas

	Group 1 (3-dose schedule)		Group 2 (2-dose schedule)		Ratio Group 2/Group 1
	N	**GMT (95% CI)**	**N**	**GMT (95% CI)**	**Ratio GMT (95% CI)**
Serotype 1	274	834 (713; 975)	282	877 (737; 1043)	1.05 (0.833; 1.33)
Serotype 2	274	879 (775; 997)	282	870 (758; 1000)	0.990 (0.821; 1.19)
Serotype 3	274	620 (545; 704)	282	602 (529; 686)	0.972 (0.810; 1.17)
Serotype 4	274	527 (467; 595)	282	507 (451; 570)	0.963 (0.814; 1.14)

Group 1 (3-dose schedule): Vaccine at D0, M6 and M12

Group 2 (2-dose schedule): Placebo at D0, vaccine at M6 and M12

For each serotype, non-inferiority was demonstrated if the lower limit of the two-sided 95% CI for the ratio was greater than 1/2.

3.5 Long-term persistence of antibodies

A decrease in the GMTs against all 4 serotypes was observed one year after the third dose. Then, GMTs stabilized over the next 2 to 4 years and remained superior to pre-vaccination GMTs. The GMTs levels depended on age and dengue serostatus at baseline.
In a Phase II study (CYD65) comparing 2 and 3-dose schedules, non-inferiority was demonstrated on antibody persistence between the 2-dose and 3-dose schedule up to 1 year after the last dose in subjects 9 years of age and above.

5.2 Pharmacokinetic properties

No pharmacokinetic studies have been performed on the Dengvaxia.

5.3 Preclinical safety data

Non-clinical safety data revealed no special risks for humans based on a repeated-dose toxicityincluding assessment of local tolerance, and a developmental and reproductive toxicology program. There was no shedding of Dengvaxia RNA in a distribution and shedding study, hence no risk of dissemination to the environment or transmission from vaccinees. A neurovirulence study shows that CYD dengue vaccine is not neurotoxic**.**

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Essential amino acids including L-Phenylalanine
Non-essential amino acids
Arginine hydrochloride
Sucrose
Trehalose dihydrate
Sorbitol (E420)
Trometamol
Urea
Hydrochloric acid and sodium hydroxide for pH adjustment
Solvent:
Sodium chloride
Water for injections

6.2 Incompatibilities

Dengvaxia must not be mixed with any other vaccine or medicinal product.

6.3 Shelf-life

Shelf-life: 3 years (36 months).

After reconstitution with the solvent provided, Dengvaxia should be used immediately.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

Do not freeze.

Store in the outer carton in order to protect from light.

For storage conditions after reconstitution of Dengvaxia, see Section 6.3.

6.5 Nature and contents of container

- [Powder (1 dose) in vial + 0.5 mL of solvent in a pre-filled syringe with 2 separate needles] – pack size of 1 or 10.

The tip caps of the pre-filled syringes contain a natural rubber latex derivative.

6.6 Special precautions for disposal and other handling

Contact with disinfectants is to be avoided since they may inactivate the vaccine viruses.

Dengvaxia must be reconstituted prior to administration.

Dengvaxia is reconstituted by transferring all of the solvent (0.4% sodium chloride solution) provided in the blue-labeled pre-filled syringe into the vial of freeze-dried powder with a yellowish green flip-off cap.

1. 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. Transfer the entire content of the pre-filled syringe into the vial containing the powder.

3. Swirl gently until the powder is completely dissolved.

The suspension should be visually inspected prior to administration. After reconstitution, Dengvaxia is a clear, colorless liquid with the possible presence of white to translucent particles (of endogenous nature).

After complete dissolution, a 0.5 mL dose of the reconstituted suspension is withdrawn into the same syringe. For injection, the syringe should be fitted with a new sterile needle.

After reconstitution with the solvent provided, Dengvaxia must be used immediately.

Any unused product or waste material should be disposed of in accordance with local regulations.

7 MARKETING AUTHORISATION HOLDER

SANOFI PASTEUR LTD.

8 MARKETING AUTHORISATION NUMBER(S)

2C 3/59 (NBC)

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30/09/2016

10 DATE OF REVISION OF THE TEXT

06/2020