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.

No adjuvants and no preservatives are added.

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, and may form a ring-shaped cake.

The solvent is a clear, colorless liquid.

4 CLINICAL PARTICULARS

studies later up to 60yr old >>see p12

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 12 through 45 years of age living in endemic areas (see Section 4.2).

4.2 Posology and method of administration

Posology

Primary vaccination

The primary vaccination schedule consists of 3 injections of one reconstituted dose (0.5 mL) to be administered at 6-month intervals.

If flexibility in the vaccination schedule is necessary, a time window of +/- 20 days is acceptable (see Section 5.1).

Paediatric population

The vaccination schedule and dose are the same for adults and for the paediatric population.

Dengvaxia should not be administered in Singapore in individuals less than 12 years of age as available clinical data are not sufficient to conclude on the benefit/risk of vaccination with Dengvaxia in this population.

Singaporean population with unknown history of prior dengue exposure

For Singaporean population with unknown history of prior dengue exposure, serostatus testing if available may provide some additional information to inform the benefit/risk considerations following vaccination with Dengvaxia in these individuals. Please refer to Section 5.1, *Singaporean population (data from CYD28 study)* subsection.

Booster dose

The need for a booster dose after primary vaccination with Dengvaxia has not been established.

Method of administration

Once the freeze-dried vaccine has been completely reconstituted using the solvent provided, it is administered by subcutaneous (SC) injection. The recommended injection site is the deltoid region.

Precautions to be taken before handling or administering the medicinal product

Do not administer by intravascular injection.
Dengvaxia must not be mixed with any other injectable vaccine(s) or medicinal product(s).

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

4.3 Contraindications

Dengvaxia must not be administered to individuals with a history of severe allergic reaction to any component of Dengvaxia or after prior administration of Dengvaxia or a vaccine containing the same components.

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

Dengvaxia must not be administered to individuals with congenital or acquired immune deficiency that impairs cell-mediated immunity, including immunosuppressive therapies such as chemotherapy or high doses of systemic corticosteroids generally given for 2 weeks or more.

Dengvaxia must not be administered to individuals with symptomatic HIV infection or with asymptomatic HIV infection when accompanied by evidence of impaired immune function.

Dengvaxia must not be administered to pregnant women.

Dengvaxia must not be administered to breastfeeding women.

4.4 Special warnings and precautions for use

As with any vaccine, vaccination with Dengvaxia may not protect 100% of vaccinated individuals. It is recommended to continue personal protection measures against mosquito bites after vaccination.

In individuals who have a history of serious or severe reactions within 48 hours after a prior administration of Dengvaxia or of a vaccine containing similar components, the risks and benefits of administering Dengvaxia must be carefully considered.

Before administering any biological, the person responsible for administration must take all precautions to prevent allergic or other reactions. As with all injectable vaccines, appropriate medical treatment and supervision must always be readily available in the event of an anaphylactic reaction following administration of the vaccine. Epinephrine (1:1000) and other appropriate agents used to control immediate allergic reactions must be available to treat unexpected events such as anaphylaxis.

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.

For patients receiving treatment with high doses of systemic corticosteroids given for 2 weeks or more (daily receipt of prednisone or equivalent 20 mg or 2 mg/kg body weight is considered as a substantially immunosuppressive dose), it is advisable to wait until immune function has recovered, i.e., for at least 4 weeks after stopping treatment, before administering Dengvaxia.

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).

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

No studies have been performed on the interference of the vaccine with laboratory and/or diagnostic tests.

4.5 Interaction with other medicinal products and other forms of interaction

Dengvaxia must not be mixed with any other injectable vaccine(s) or medicinal product(s).

Separate syringes and needles, separate injection sites and preferably separate limbs must be used if any other vaccine(s) or medicinal product(s) is/are concomitantly administered.

No specific studies have been performed on concomitant administration of the vaccine with any other medicinal product(s) in individuals 12 through 45 years of age living in endemic areas.

For patients receiving treatment with immunoglobulins or blood products containing immunoglobulins, such as blood or plasma, it is advisable 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.

For immunosuppressive therapy or corticosteroid therapy, see Sections 4.3 and 4.4.

4.6 Fertility, pregnancy and lactation

Pregnancy

Pregnancy constitutes a contraindication (see Section 4.3).
Women of childbearing age should avoid becoming pregnant for 4 weeks after receiving any injection of Dengvaxia.
Animal studies did not indicate any direct or indirect harmful effects with respect to reproductive toxicity (see Section 5.3).

Breastfeeding

Dengvaxia is contraindicated during breastfeeding (see Section 4.3).
It is not known whether this vaccine is excreted into human milk. The effect on breastfed infants of administration of Dengvaxia to their mothers has not been studied.
Animal studies did not indicate any direct or indirect harmful effects with respect to lactation (see Section 5.3).

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

No studies have been performed on the effects of the vaccine on the ability to drive or to use machines.

4.8 Undesirable effects

Summary of the safety profile

A total of approximately 20,667 subjects 9 through 60 years of age received at least one injection of the final formulation of the vaccine according to the claimed vaccination schedule in 13 randomized, observer-blinded, placebo-controlled Phase II to Phase III clinical studies.

The safety profile presented below is based on a pooled analysis including a total of 1547 subjects 18 through 60 years of age and 19,120 subjects 9 through 17 years of age. Reactogenicity was assessed in a subset of 4615 subjects, including 1547 subjects 18 through 60 years of age and 3068 subjects 9 through 17 years of age.

Safety was monitored during the first 28 days following each injection in the reactogenicity subset, and serious adverse events (SAEs), including dengue cases, were collected throughout the studies in all subjects, up to at least 6 months after the last injection of the vaccine.

In subjects 9 through 60 years of age, the most frequently reported ARs following any injection of the vaccine were headache, injection site pain, malaise and myalgia.

The ARs were usually mild to moderate in severity and of short duration (0 to 3 days). Onset was typically observed 0 to 3 days after the injection, except for fever which appeared within 14 days after the injection.

Systemic ARs tended to be less frequent after the second and third injections as compared to the first injection.

Tabulated list of adverse reactions

Adverse reactions are listed according to the following frequency categories:
Very common: ≥ 1/10 (≥ 10%)
Common: ≥ 1/100 to < 1/10 (≥ 1% and < 10%)
Uncommon: ≥ 1/1000 to < 1/100 (≥ 0.1% and < 1%)
Rare: ≥ 1/10,000 to < 1/1000 (≥ 0.01% and < 0.1%)

ARs within 28 days after any injection in subjects 9 through 60 years of age are presented in Table 1, based on safety data collected during clinical studies.

Table 1: Adverse Reactions from Clinical Studies - Subjects 9 through 60 years of age

System-organ Class	Very Common (≥ 10%)	Common (≥ 1% and < 10%)	Uncommon (≥ 0.1% and < 1%)
Infections and infestations			Upper respiratory tract infection
Blood and lymphatic tissue disorders			Lymphadenopathy
Nervous system disorders	Headache		Dizziness, Migraine
Respiratory, thoracic and mediastinal disorders			Oropharyngeal pain, Cough, Rhinorrhoea
Gastrointestinal disorders			Nausea
Skin and subcutaneous tissue disorders			Rash, Urticaria
Musculoskeletal and connective tissue disorders	Myalgia		Neck pain, Arthralgia
General disorders and administration site conditions	Injection site pain, Malaise, Asthenia, Fever	Injection site reactions (erythema, hematoma, swelling, pruritus)	Injection site induration, Influenza-like illness

"Very common" and "common" ARs were similar in nature for subjects 9 through 17 years of age and subjects 18 through 60 years of age, however there were differences in terms of frequency. Fever was less frequently reported in subjects 18 through 60 years of age (frequency: common) and injection site haematoma and pruritus were less frequently reported in subjects 9 through 17 years of age (frequency: uncommon).

"Uncommon" ARs were observed with the following age-group specificities:

- Lymphadenopathy, migraine, arthralgia and influenza-like illness were only reported in subjects 18 through 60 years of age;
- Urticaria was only reported in subjects 9 through 17 years of age;
- Upper respiratory tract infection, dizziness, oropharyngeal pain, cough, rhinorrhoea, nausea, rash and neck pain were less frequently reported in subjects 9 through 17 years of age (frequency: rare or very rare, i.e., with a frequency < 0.1%).

In phase III efficacy studies (CYD14 and CYD15), isolated neurological disorder related SAEs have been observed in subjects 8 through 11 years of age: acute polyneuropathy in one subject of 10 years of age, convulsion (reported as "seizures not specified") in one subject of 11 years of age, and acute disseminated encephalomyelitis (ADEM) in one subject aged 8 years of age. These events were isolated and therefore not listed in the tabulated list of adverse reactions above. These three isolated events were outside the age indication.

Long-term safety follow-up data

SAEs have been collected and followed-up for at least two years after the third injection in pivotal efficacy studies described in Section 5.1.
In subjects 9 years of age and older, no difference in the safety profile was observed from the long-term follow-up data.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the Health Sciences Agency of Singapore via the ADR online reporting tool at www.hsa.gov.sg or to Sanofi Singapore Pharmacovigilance at PV.SIN@sanofi.com.

4.9 Overdose

No cases of overdose have been reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Viral vaccines

ATC code: J07BX

J (ANTIINFECTIVES FOR SYSTEMIC USE) 07 (VACCINES) B (VIRAL VACCINES) X (Other viral vaccines)

Mechanism of action

The vaccine 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.

Immunogenicity

Immunogenicity data were collected in a total of approximately 1800 subjects 12 through 45 years of age from endemic areas who received at least one injection of the final formulation of the vaccine according to the claimed vaccination schedule in 7 randomized, observer-blinded, placebo-controlled Phase II to Phase III clinical studies. Most of the subjects were 12 through 16 years of age (n= 1492).

The immunogenicity data presented correspond to the neutralizing antibody titers for each serotype as measured with the plaque reduction neutralization test (PRNT). The results are presented as geometric mean titers (GMTs), expressed in reciprocal dilutions (1/dil), measured at baseline and 28 days after the third injection of the vaccine.

GMT data on subjects 17 through 25 and 26 through 45 years of age included in Phase II safety and immunogenicity studies conducted in endemic areas (CYD22, CYD28 and CYD47) and on subjects 12 through 16 years of age included in the 2 large-scale Phase III efficacy studies, CYD14 and CYD15, and in CYD28 conducted in Singapore are presented by study and region in Table 2.

Table 2: Dengue immunogenicity data pre-injection 1 and 28 days post-injection 3 - GMTs of antibodies against each serotype (1/dil) - Dengue PRNT – Subjects 12 through 45 years of age in endemic areas

			Serotype 1			Serotype 2			Serotype 3			Serotype 4		
Age group	**Region**	**Study**	**N**	**Pre-injection 1 GM (95% CI)**	**Post-injection 3 GM (95% CI)**	**N**	**Pre-injection 1 GM (95% CI)**	**Post-injection 3 GM (95% CI)**	**N**	**Pre-injection 1 GM (95% CI)**	**Post-injection 3 GM (95% CI)**	**N**	**Pre-injection 1 GM (95% CI)**	**Post-injection 3 GM (95% CI)**
Subjects 26 through 45 years of age	**Asia Pacific**	**CYD22**	10	467 (229; 955)	681 (257; 1808)	10	393 (191; 811)	578 (341; 980)	10	245 (142; 422)	461 (313; 678)	10	105 (34.4; 318)	323 (179; 582)
		CYD28	91	22.5 (14.9; 34.1)	58.6 (36.5; 94.2)	91	22.4 (14.9; 33.7)	76.3 (50.8; 115)	91	19.3 (13.4; 27.8)	114 (85.1; 153)	91	11.5 (8.41; 15.8)	126 (95.5; 167)
		CYD47	82	222 (143; 345)	557 (389; 798)	82	248 (159; 387)	510 (370; 704)	82	292 (192; 443)	880 (642; 1206)	82	75.0 (52.5; 107)	376 (286; 494)
Subjects 17 through 25 years of age	**Asia Pacific**	**CYD22**	10	229 (47.6; 1102)	710 (189; 2666)	10	311 (72.3; 1337)	1178 (454; 3051)	10	104 (33.6; 322)	390 (177; 858)	10	53.7 (15.8; 183)	436 (223; 850)
		CYD28	75	8.51 (6.00; 12.1)	38.7 (23.6; 63.3)	75	10.2 (6.75; 15.5)	56.6 (35.3; 90.6)	75	8.39 (6.44; 10.9)	60.0 (41.3; 87.3)	75	7.57 (5.88; 9.73)	107 (73.5; 155)
		CYD47	44	131 (65.3; 262)	328 (187; 576)	44	141 (73.8; 271)	442 (268; 727)	44	127 (66.5; 244)	481 (321; 718)	44	31.6 (19.6; 50.9)	275 (193; 391)
Subjects 12 through 16 years of age	**Asia Pacific**	**CYD14**	400	93.1 (73.5; 118)	305 (249; 372)	400	152 (121; 190)	592 (506; 692)	400	84.2 (67.6; 105)	309 (261; 367)	400	51.2 (42.4; 61.8)	213 (185; 245)
		CYD28	123	6.36 (5.21; 7.76)	26.3 (19.5; 35.6)	123	7.24 (5.75; 9.10)	46.7 (35.0; 62.2)	123	6.87 (5.77; 8.19)	71.8 (55.5; 92.9)	123	5.79 (5.11; 6.56)	78.5 (62.8; 98.1)
	Latin America	**CYD15**	658	163 (137; 194)	466 (399; 545)	658	179 (152; 211)	684 (605; 772)	658	146 (124; 171)	554 (488; 628)	658	50.4 (44.0; 57.7)	277 (252; 305)

The lower limit of quantification for dengue neutralizing antibodies is 10 (1/dil).

Endemic areas are defined as areas where the disease has been continuously present in the native population with documented outbreaks or epidemics.

CYD22: Vietnam; CYD28: Singapore; CYD47: India; CYD14: Indonesia, Malaysia, the Philippines, Thailand, Vietnam; CYD15: Brazil, Colombia, Honduras, Mexico, Puerto Rico.

In all age groups in all studies, an increase in GMTs was observed for each of the 4 serotypes 28 days after the third injection as compared to baseline, regardless of the region, i.e., Asia Pacific or Latin America.

Differences in GMTs 28 days after the third injection were observed depending on dengue immune status[a] before the first injection, the age and the region. Overall:

- The higher the GMTs before the first injection, the higher the GMTs 28 days after the third injection;
- GMTs 28 days after the third injection were higher in subjects who were dengue immune before the first injection compared to subjects who were not dengue immune before the first injection;
- Dengue immune status before the first injection is a confounding factor of age: the older the subject, the higher the GMTs before the first injection and the higher the GMTs 28 days after the third injection, i.e., the immune response in terms of GMTs 28 days after the third injection increases with age.

Singaporean Population (data from CYD28 study):

In CYD28, a clinical immunogenicity and safety study conducted in Singapore in individuals from 2 to 45 years of age, an immune response to the vaccine was observed in all age groups, with an increase of GMTs for each serotype 28 days after the third injection. Post-injection 3 GMTs in CYD28 study were lower than in the other studies conducted in highly endemic countries (see Table 2). Clinical efficacy studies have not been conducted in the Singaporean population.

Singaporean population with unknown previous history of dengue

Table 3 presents the immune response in CYD28 study, conducted in Singapore, by baseline dengue immune status. An increase in GMTs was observed 28 days after the third injection as compared to baseline in both dengue immune and non-immune subjects at baseline. GMTs 28 days after the third injection were higher in subjects who were dengue immune at baseline, as observed in the other clinical studies. Low GMTs were observed in dengue non-immune subjects at baseline. Post-injection 3 GMTs were also low in the out-of indication 2- to 5-year-old subjects included in the CYD14 Phase III study, for which the cumulative relative risk of hospitalized dengue illness was 2.177 95%CI (0.99; 5.43) non statistically significant within the 2 years of long-term follow-up (from 1 to 3 years after the third injection) and 1.2 95%CI (0.7; 2.2) non statistically significant within the first four years after the first injection.

Data collected from the immunogenicity subset and followed over the 5 years of the ongoing efficacy trials did not show evidence of enhanced risk in seronegative individuals of 12 years of age and above. In Singapore, for individuals with unknown history of prior dengue exposure, serostatus testing if available

[a] Dengue immune status at baseline (i.e. before the first injection) measured by PRNT is defined as:

- Immune: subjects with quantified (≥ 10 [1/dil], the lower limit of quantitation) neutralizing antibodies against at least one dengue serotype in the baseline sample,
- Non-immune: subjects without quantified (< the lower limit of quantitation) neutralizing antibodies against any of the 4 dengue serotypes in the baseline sample.

The terms “immune and non-immune” are used to describe the presence or not of antibodies at baseline. Immune is not used to imply that subjects are protected from dengue infection.

may provide some additional information to inform the benefit/risk considerations following vaccination with Dengvaxia in these individuals.

Table 3: Dengue immunogenicity data pre-injection 1 and 28 days post-injection 3 in CYD28 study conducted in Singapore - by baseline dengue immune status and age group - GMTs of antibodies against each serotype (1/dil) - Dengue PRNT - Subjects 12 through 45 years of age

		Serotype 1			Serotype 2			Serotype 3			Serotype 4		
Age group	**Baseline dengue immune status**	**N**	**Pre-injection 1 GM (95% CI)**	**Post-injection 3 GM (95% CI)**	**N**	**Pre-injection 1 GM (95% CI)**	**Post-injection 3 GM (95% CI)**	**N**	**Pre-injection 1 GM (95% CI)**	**Post-injection 3 GM (95% CI)**	**N**	**Pre-injection 1 GM (95% CI)**	**Post-injection 3 GM (95% CI)**
Subjects 26 through 45 years of age	**Non Immune**	37	5.00 (NC)	13.8 (9.82; 19.3)	37	5.00 (NC)	28.1 (17.8; 44.4)	37	5.00 (NC)	47.1 (35.4; 62.7)	37	5.00 (NC)	73.6 (47.4; 114)
	Immune	49	74.6 (43.1; 129)	255 (141; 463)	49	71.8 (42.4; 122)	226 (138; 372)	49	55.2 (34.6; 88.0)	261 (179; 380)	49	21.7 (13.3; 35.4)	202 (143; 287)
Subjects 17 through 25 years of age	**Non Immune**	52	5.00 (NC)	19.3 (13.1; 28.6)	52	5.00 (NC)	29.8 (20.5; 43.5)	52	5.00 (NC)	34.5 (25.1; 47.5)	52	5.00 (NC)	80.1 (50.4; 127)
	Immune	20	33.9 (11.4; 101)	215 (64.0; 723)	20	66.0 (19.7; 221)	282 (88.1; 905)	20	32.2 (16.4; 63.1)	233 (101; 534)	20	22.2 (10.5; 47.2)	240 (134; 431)
Subjects 12 through 16 years of age	**Non Immune**	106	5.00 (NC)	19.6 (15.3; 25.1)	106	5.00 (NC)	36.3 (28.1; 47.0)	106	5.00 (NC)	56.7 (44.6; 72.1)	106	5.00 (NC)	68.9 (54.3; 87.4)
	Immune	16	31.7 (7.74; 130)	195 (49.1; 779)	16	85.7 (23.5; 313)	265 (80.6; 870)	16	56.5 (25.4; 126)	347 (138; 874)	16	15.3 (6.34; 37.1)	204 (128; 327)

The lower limit of quantification for dengue neutralizing antibodies is 10 (1/dil).

Adult Population from 46 to 60 years of age

A study was conducted in adult subjects aged 18 to 60 years in Australia in non-endemic areas. This study included 241 subjects aged 46 through 60 years of age. A similar immune response was observed in 18 to 45 and 46 to 60-year-old subjects included in the trial against the 4 serotypes: in subjects aged 46 to 60 years, GMTs post-injection 3 were of 17.6 (1/dil) for serotype 1, 54.2 (1/dil) for serotype 2, 83.3 (1/dil) for serotype 3 and 144 (1/dil) for serotype 4.

Data on long-term persistence of antibodies

GMT data up to 4 years after the last injection are presented by age group and by study in Table 4 for serotype 1 and 2 and Table 5 for serotype 3 and 4.

Overall, in subjects 12 years of age and older in endemic areas, a decrease in the GMTs against all 4 serotypes was observed one year after the third injection and then a trend toward stabilization was observed in the subsequent years. The decrease in GMTs was variable depending on age and the dengue immune status of subjects before the first injection. Long-term GMTs for each serotype remained higher than GMTs before the first injection.

Table 4: Dengue immunogenicity data up to 4 years after the last injection for serotype 1 and 2 - GMTs of antibodies against each serotype (1/dil) - Dengue PRNT - Subjects 12 through 45 years of age

		Serotype 1							Serotype 2						
Age group	**Study**	**N**	**Pre-dose 1 GM (95% CI)**	**Post-dose 3 GM (95% CI)**	**Year 1 GM (95% CI)**	**Year 2 GM (95% CI)**	**Year 3 GM (95% CI)**	**Year 4 GM (95% CI)**	**N**	**Pre-dose 1 GM (95% CI)**	**Post-dose 3 GM (95% CI)**	**Year 1 GM (95% CI)**	**Year 2 GM (95% CI)**	**Year 3 GM (95% CI)**	**Year 4 GM (95% CI)**
26-45 years	**CYD22**	10	467 (229; 955)	681 (257; 1808)	351 (151; 819)	407 (177; 938)	434 (193; 979)	309 (141; 674)	10	393 (191; 811)	578 (341; 980)	724 (374; 1402)	634 (304; 1323)	366 (197; 682)	540 (324; 900)
	CYD28	91	22.5 (14.9; 34.1)	58.6 (36.5; 94.2)	36.3 (22.2; 59.3)	33.2 (20.4; 54.0)	30.2 (18.0; 50.7)	28.9 (17.5; 47.9)	91	22.4 (14.9; 33.7)	76.3 (50.8; 115)	65.3 (41.1; 104)	90.0 (52.9; 153)	47.8 (29.7; 77.0)	42.9 (27.1; 68.0)
17-25 years	**CYD22**	10	229 (47.6; 1102)	710 (189; 2666)	300 (68.6; 1312)	212 (42.2; 1068)	203 (39.1; 1051)	201 (38.4; 1053)	10	311 (72.3; 1337)	1178 (454; 3051)	588 (125; 2754)	558 (183; 1706)	422 (101; 1772)	398 (96.1; 1650)
	CYD28	75	8.51 (6.00; 12.1)	38.7 (23.6; 63.3)	14.1 (8.51; 23.5)	16.1 (9.06; 28.7)	14.2 (7.97; 25.4)	15.3 (7.69; 30.5)	75	10.2 (6.75; 15.5)	56.6 (35.3; 90.6)	27.6 (16.2; 47.0)	33.3 (19.2; 57.7)	22.5 (12.5; 40.3)	18.7 (10.6; 33.0)
12-16 years	**CYD14**	400	93.1 (73.5; 118)	305 (249; 372)	247 (198; 308)	217 (173; 271)	No data*	No data*	400	152 (121; 190)	592 (506; 692)	425 (357; 505)	324 (272; 386)	No data*	No data*
	CYD22	20	59.9 (17.7; 203)	192 (68.6; 536)	128 (43.3; 377)	113 (37.1; 346)	124 (36.0; 427)	110 (34.2; 354)	20	83.2 (29.5; 235)	334 (132; 845)	324 (103; 1023)	493 (166; 1465)	120 (43.5; 332)	165 (57.0; 479)
	CYD28	123	6.36 (5.21; 7.76)	26.3 (19.5; 35.6)	9.28 (7.23; 11.9)	7.65 (6.18; 9.47)	7.51 (5.98; 9.43)	6.61 (5.53; 7.89)	123	7.24 (5.75; 9.10)	46.7 (35.0; 62.2)	16.1 (11.9; 21.9)	17.8 (13.3; 23.9)	12.7 (9.53; 16.9)	13.3 (9.82; 18.0)
	CYD15	658	163 (137; 194)	466 (399; 545)	343 (289; 409)	254 (214; 301)	No data*	No data*	658	179 (152; 211)	684 (605; 772)	472 (410; 542)	415 (364; 475)	No data*	No data*

*Study ongoing. No data available
The lower limit of quantification for dengue neutralizing antibodies is 10 (1/dil).
CYD22: Vietnam; CYD28: Singapore; CYD14: Indonesia, Malaysia, the Philippines, Thailand, Vietnam; CYD15: Brazil, Colombia, Honduras, Mexico, Puerto Rico.

Table 5: Dengue immunogenicity data up to 4 years after the last injection for serotype 3 and 4 - GMTs of antibodies against each serotype (1/dil) - Dengue PRNT - Subjects 12 through 45 years of age

		Serotype 3							Serotype 4						
Age group	**Study**	**N**	**Pre-dose 1 GM (95% CI)**	**Post-dose 3 GM (95% CI)**	**Year 1 GM (95% CI)**	**Year 2 GM (95% CI)**	**Year 3 GM (95% CI)**	**Year 4 GM (95% CI)**	**N**	**Pre-dose 1 GM (95% CI)**	**Post-dose 3 GM (95% CI)**	**Year 1 GM (95% CI)**	**Year 2 GM (95% CI)**	**Year 3 GM (95% CI)**	**Year 4 GM (95% CI)**
26-45 years	**CYD22**	10	245 (142; 422)	461 (313; 678)	860 (562; 1316)	360 (227; 571)	230 (138; 385)	205 (160; 264)	10	105 (34.4; 318)	323 (179; 582)	283 (130; 618)	128 (69.3; 237)	144 (73.8; 282)	109 (67.3; 178)
	CYD28	91	19.3 (13.4; 27.8)	114 (85.1; 153)	60.7 (39.9; 92.4)	88.0 (59.9; 129)	58.9 (37.0; 93.6)	31.9 (20.7; 49.1)	91	11.5 (8.41; 15.8)	126 (95.5; 167)	86.0 (63.3; 117)	57.5 (41.6; 79.4)	53.2 (39.1; 72.3)	36.6 (26.9; 49.7)
17-25 years	**CYD22**	10	104 (33.6; 322)	390 (177; 858)	571 (215; 1518)	208 (61.3; 703)	149 (44.6; 495)	106 (30.8; 365)	10	53.7 (15.8; 183)	436 (223; 850)	254 (104; 624)	163 (43.9; 608)	110 (36.7; 327)	84.8 (25.4; 283)
	CYD28	75	8.39 (6.44; 10.9)	60.0 (41.3; 87.3)	25.8 (16.4; 40.6)	31.4 (18.9; 52.2)	26.6 (15.5; 45.6)	20.0 (12.1; 33.1)	75	7.57 (5.88; 9.73)	107 (73.5; 155)	41.5 (27.2; 63.3)	38.9 (24.7; 61.2)	28.4 (18.7; 43.0)	22.3 (14.6; 34.2)
12-16 years	**CYD14**	400	84.2 (67.6; 105)	309 (261; 367)	350 (290; 422)	224 (185; 272)	No data*	No data*	400	51.2 (42.4; 61.8)	213 (185; 245)	146 (127; 169)	132 (115; 153)	No data*	No data*
	CYD22	20	36.3 (17.1; 76.9)	135 (66.9; 274)	323 (131; 795)	155 (73.5; 327)	56.9 (26.2; 123)	56.5 (26.2; 122)	20	26.9 (12.2; 59.2)	183 (87.0; 385)	166 (73.1; 377)	127 (69.4; 233)	57.3 (31.1; 105)	36.5 (19.0; 70.1)
	CYD28	123	6.87 (5.77; 8.19)	71.8 (55.5; 92.9)	18.9 (14.3; 25.1)	20.3 (15.3; 26.9)	14.9 (11.4; 19.5)	13.5 (10.5; 17.5)	123	5.79 (5.11; 6.56)	78.5 (62.8; 98.1)	31.2 (24.2; 40.3)	34.2 (25.8; 45.2)	24.1 (18.7; 31.1)	21.3 (16.5; 27.6)
	CYD15	658	146 (124; 171)	554 (488; 628)	356 (309; 411)	348 (304; 397)	No data*	No data*	658	50.4 (44.0; 57.7)	277 (252; 305)	214 (193; 237)	157 (141; 174)	No data*	No data*

*Study ongoing. No data available
The lower limit of quantification for dengue neutralizing antibodies is 10 (1/dil).
CYD22: Vietnam; CYD28: Singapore; CYD14: Indonesia, Malaysia, the Philippines, Thailand, Vietnam; CYD15: Brazil, Colombia, Honduras, Mexico, Puerto Rico.

Efficacy:

The efficacy of the vaccine was assessed in 2 pivotal, large-scale, randomized, observer-blinded, placebo-controlled Phase III efficacy studies conducted in 5 countries each, CYD14 in Asia and CYD15 in Latin America.

In the 2 pivotal Phase III studies, efficacy was assessed in a total of 13,732 subjects 12 through 16 years of age who received at least one injection of the vaccine: 2329 subjects 12 through 14 years of age in CYD14 and the 11,400 subjects 12 through 16 years of age in CYD15. A time window of +/- 20 days was applied for the second and third injections. More than 70% of subjects were dengue immune at baseline.

In subjects 12 through 16 years of age, the efficacy of the vaccine against symptomatic virologically confirmed dengue (VCD) cases due to any and each of the 4 serotypes was demonstrated in both studies, CYD14 and CYD15, and in the meta-analysis. The assessment period extended from the first injection to the end of the active phase, i.e. over the 25-month period after the first injection.

The efficacy of the vaccine against severe VCD cases and against hospitalized VCD cases (i.e., hospital admission due to dengue, whatever the severity) were also evaluated. For severe VCD cases, two types of endpoints were considered: clinically severe VCD cases and VCD cases that met WHO criteria for dengue hemorrhagic fever (DHF). Vaccine efficacy was demonstrated for these three endpoints in both studies and in the meta-analysis.

The efficacy results in subjects 12 through 16 years of age are presented in Table 6 for each of the two phase III efficacy studies and in the meta-analysis. The results are presented for the entire active phase of 25 months.

Table 6: Vaccine efficacy estimates in subjects 12 through 16 years of age from a meta-analysis of phase III efficacy study data over the 25-month period after the first injection

	CYD14 VE % (95% CI)*	CYD15 VE % (95% CI)*	CYD14+CYD15 VE % (95% CI)*
Any serotype	74.4 (59.2; 84.3)	67.6 (59.3; 74.3)	69.2 (62.4; 74.8)
Serotype 1	74.4 (48.1; 88.0)	54.4 (32.9; 69.1)	60.4 (45.4; 71.3)
Serotype 2	50.5 (-32.6; 81.5)	53.8 (26.4; 71.1)	53.2 (30.5; 68.4)
Serotype 3	78.7 (6.8; 96.5)	75.7 (57.5; 86.5)	76.2 (60.8; 85.5)
Serotype 4	93.0 (69.3; 99.2)	86.5 (74.8; 93.3)	88.0 (78.9; 93.2)
Clinically severe VCD cases	100.0 (-20.2; 100.0)	93.8 (53.4; 99.9)	95.5 (64.8; 99.4)
DHF meeting any WHO criteria	100.0 (-20.2; 100.0)	92.9 (44.5; 99.8)	95.0 (61.0; 99.4)
Hospitalized VCD	86.5 (48.9; 97.6)	78.6 (51.3; 91.4)	81.3 (63.8; 90.4)

* The efficacy of the vaccine is considered as significant if the lower bound of the 95% CI is greater than 0.
CI: confidence interval.

Vaccine efficacy against VCD was demonstrated in both dengue immune subjects at baseline (81.9%, 95%CI 67.2; 90.0) and dengue non-immune subjects at baseline (52.5%, 95% CI: 5.9; 76.1) aged 9 to 16 years.

Bridging of efficacy data to individuals 17 through 45 years of age in endemic areas

The 2 pivotal efficacy studies showed that higher post-injection 3 GMTs were associated with higher protection.

Based on immunogenicity data from Phase II studies conducted in Asia (CYD22 conducted in Vietnam in 180 subjects 2 through 45 years of age including 30 adults, and CYD47, conducted in India in 189 subjects 18 through 45 years of age), similar or higher neutralizing antibody levels after the third injection are anticipated in adults from endemic areas, and thus a similar or higher level of protection after the third injection of the vaccine is expected in individuals 17 through 45 years of age in endemic areas compared to the vaccine efficacy observed in the CYD14 and CYD15 studies.

Long-term follow-up data from Phase III studies in subjects aged 12 to 16 years.

In CYD14 and CYD15, during the first 2 years of long-term follow-up[a], 15 hospitalized VCD cases were reported in 8705 vaccinees versus 22 hospitalized VCD cases reported in 4358 subjects in the control group (with a 2:1 randomization ratio).
Overall, from the first injection to 3 years after the third injection, 27 hospitalized VCD cases were reported in 8879 vaccinees versus 53 hospitalized VCD cases reported in 4436 subjects in the control group (with a 2:1 randomization ratio).

5.2 Pharmacokinetic properties

No pharmacokinetic studies have been performed on the vaccine.

5.3 Preclinical safety data

Non-clinical safety data revealed no special risks for humans based on a repeated-dose toxicity and local tolerance study, a distribution and shedding study, a neurovirulence study and a developmental and reproductive toxicology program.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder:
Essential amino acids including L-Phenylalanine
Non-essential amino acids
L-Arginine hydrochloride
Sucrose
D-Trehalose dihydrate
D-Sorbitol
Trometamol
Urea

[a] The long-term follow-up period started at the end of the Active Phase, i.e. 25 months after the first injection

Solvent for reconstitution:
Sodium chloride
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, Dengvaxia must not be mixed with any other injectable vaccine(s) or medicinal product(s).

6.3 Shelf-life

Shelf-life: 3 years (36 months).

After reconstitution with the solvent provided, Dengvaxia should be used immediately. However, in-use stability studies have shown that the reconstituted vaccine can be kept for up to 6 hours between 2°C and 8°C (i.e., in a refrigerator) and protected from light.

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.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

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

Separate syringes and needles, separate injection sites and preferably separate limbs must be used if any other vaccine(s) or medicinal product(s) is/are concomitantly administered.

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. The pre-filled syringe is fitted with a sterile needle for this transfer. The vial is then gently swirled. 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.

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

Any unused product or waste material should be disposed of, preferably by heat inactivation or incineration, in accordance with local regulations.

7 MARKETING AUTHORISATION HOLDER

Sanofi-aventis Singapore Pte Ltd,
38 Beach Road #18-11,
South Beach Tower,
Singapore 189767

8 MARKETING AUTHORISATION NUMBER(S)

Not applicable.

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Not applicable.

10 DATE OF REVISION OF THE TEXT

Not applicable.