



Clinical trial results:

A Study of Dengue Vaccine in Healthy Toddlers Aged 12 to 15 Months in the Philippines

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2014-001694-14 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 08 May 2012 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 (current) |
| This version publication date | 16 February 2016 |
| First version publication date | 31 July 2015 |

Trial information

Trial identification

| | |
|-----------------------|-------|
| Sponsor protocol code | CYD08 |
|-----------------------|-------|

Additional study identifiers

| | |
|------------------------------------|-----------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01064141 |
| WHO universal trial number (UTN) | U1111-1111-5855 |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Sanofi Pasteur SA |
| Sponsor organisation address | 2, avenue Pont Pasteur, Lyon Cedex 07, France, F-69367 |
| Public contact | Senior Director, Clinical Development, Sanofi Pasteur SA, 65 6431 2358, Anh.Wartel-Tram@sanofipasteur.com |
| Scientific contact | Senior Director, Clinical Development, Sanofi Pasteur SA, 65 6431 2358, Anh.Wartel-Tram@sanofipasteur.com |

Notes:

Paediatric regulatory details

| | |
|--|---------------------|
| Is trial part of an agreed paediatric investigation plan (PIP) | Yes |
| EMA paediatric investigation plan number(s) | EMA-001201-PIP01-11 |
| Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial? | No |
| Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial? | Yes |

Notes:

Results analysis stage

| | |
|--|--------------|
| Analysis stage | Final |
| Date of interim/final analysis | 31 July 2012 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|-------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 08 May 2012 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Safety of CYD dengue vaccine after each injection; first injection given alone or co-administered with measles, mumps, rubella (MMR) vaccine (Trimovax).

Dengue vaccinal viremia

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were randomized and vaccinated in the study. Vaccinations were performed by qualified and trained study personnel. Subjects with allergy to any of the vaccine components were not vaccinated. After vaccination, subjects were also kept under clinical observation for 30 minutes to ensure their safety. Appropriate medical equipment was also available on site in case of any immediate allergic reactions.

Background therapy:

Not applicable

Evidence for comparator:

Not applicable

| | |
|---|-----------------|
| Actual start date of recruitment | 18 January 2010 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------|
| Country: Number of subjects enrolled | Philippines: 210 |
| Worldwide total number of subjects | 210 |
| EEA total number of subjects | 0 |

Notes:

Subjects enrolled per age group

| | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 210 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |

| | |
|---------------------|---|
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Study subjects were enrolled from 18 January 2010 to 29 September 2010 at 2 clinical centers in the Philippines.

Pre-assignment

Screening details:

A total of 210 subjects who met all of the inclusion criteria and none of the exclusion criteria were enrolled and randomized.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Double blind |
| Roles blinded | Subject, Investigator |

Blinding implementation details:

For all groups, the first injection of CYD dengue vaccine was performed under a modified double-blind process where only the person who administered the injection knew which product had been administered. To maintain the modified double-blind process for the sequential versus co-administration of MMR with the first injection of CYD dengue vaccine, some of the toddlers received one injection of placebo.

Arms

| | |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes |
| Arm title | Group 1 |

Arm description:

Subjects received a total of 5 injections (Dengue vaccine): First injection - Measles, mumps, rubella (MMR) vaccine (Month-1); Second injection - Dengue vaccine (M0), Third injection - Dengue vaccine (M0+6 months); Fourth injection - Diphtheria, Tetanus, Pertussis, Poliomyelitis, and Hib vaccine (M0+9 months), and Fifth injection - Dengue vaccine (M0+12 months).

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | CYD Dengue Vaccine |
| Investigational medicinal product code | 323 |
| Other name | |
| Pharmaceutical forms | Powder and solvent for suspension for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

0.5 mL, subcutaneous, 1 injection at M0, M0+6 months, and M0+12 months.

| | |
|--|--|
| Investigational medicinal product name | MMR Vaccine (TRIMOVAX®) |
| Investigational medicinal product code | 065 |
| Other name | |
| Pharmaceutical forms | Powder and suspension for suspension for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

0.5 mL, subcutaneous use, 1 injection at Month-1.

| | |
|--|--|
| Investigational medicinal product name | PENTAXIM® |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and suspension for suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

0.5 mL, intramuscular use, 1 injection at M0+9 months.

| | |
|------------------|---------|
| Arm title | Group 2 |
|------------------|---------|

Arm description:

Subjects received a total of 5 injections (control): First injection - MMR (Month-1); Second injection; control Varicella vaccine (M0); Third injection; control Hepatitis A vaccine (M0 + 6 months); Fourth injection; Diphtheria, Tetanus, Pertussis, Poliomyelitis, and Hib vaccine (M0 + 9 months), and Fifth injection - control Hepatitis A vaccine (M0+12 months).

| | |
|--|--|
| Arm type | Active comparator |
| Investigational medicinal product name | MMR Vaccine (TRIMOVAX®) |
| Investigational medicinal product code | 065 |
| Other name | |
| Pharmaceutical forms | Powder and suspension for suspension for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

0.5 mL, subcutaneous use, 1 injection at Month-1.

| | |
|--|--|
| Investigational medicinal product name | PENTAXIM® |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and suspension for suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

0.5 mL, intramuscular use, 1 injection at M0+9 months.

| | |
|--|---|
| Investigational medicinal product name | OKAVAX® |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and solvent for suspension for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

0.5 mL, subcutaneous use, 1 injection at M0.

| | |
|--|--------------------------|
| Investigational medicinal product name | AVAXIM® 80U |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Suspension for injection |
| Routes of administration | Intramuscular use |

Dosage and administration details:

0.5 mL, intramuscular use, 1 injection at M0+6 months and M0+12 months.

| | |
|------------------|---------|
| Arm title | Group 3 |
|------------------|---------|

Arm description:

Subjects received a total of 6 injections: First injection - control Varicella vaccine (Month-1); Second Dengue vaccine and third MMR injections (M0); Fourth injection; Dengue vaccine (M0+6 months); Fifth injection - Diphtheria, Tetanus, Pertussis, Poliomyelitis, and Hib vaccine (M0+9 months), and Sixth injection; Dengue vaccine (M0+12 months).

| | |
|--|---|
| Arm type | Experimental |
| Investigational medicinal product name | CYD Dengue Vaccine |
| Investigational medicinal product code | 323 |
| Other name | |
| Pharmaceutical forms | Powder and solvent for suspension for injection |
| Routes of administration | Subcutaneous use |

| | |
|---|--|
| Dosage and administration details: | |
| 0.5 mL, subcutaneous, 1 injection at M0, M0+6 months, and M0+12 months. | |
| Investigational medicinal product name | OKAVAX® |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and solvent for suspension for injection |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: | |
| 0.5 mL, subcutaneous use, 1 injection at Month-1. | |
| Investigational medicinal product name | PENTAXIM® |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and suspension for suspension for injection |
| Routes of administration | Intramuscular use |
| Dosage and administration details: | |
| 0.5 mL, intramuscular use, 1 injection at M0+9 months. | |
| Investigational medicinal product name | MMR vaccine (TRIMOVAX®) |
| Investigational medicinal product code | 065 |
| Other name | |
| Pharmaceutical forms | Powder and suspension for suspension for injection |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: | |
| 0.5 mL, subcutaneous use, 1 injection at M0. | |
| Arm title | Group 4 |
| Arm description: | |
| Subjects received a total of 6 injections (sequential administration): First injection - MMR (Month-1); Second Dengue vaccine and third placebo injections (M0); Fourth injection - Dengue vaccine (M0+6 months); Fifth injection - Diphtheria, Tetanus, Pertussis, Poliomyelitis, and Hib vaccine (M0+9 months), and Sixth injection - Dengue vaccine (M0+12 months) | |
| Arm type | Experimental |
| Investigational medicinal product name | CYD Dengue Vaccine |
| Investigational medicinal product code | 323 |
| Other name | |
| Pharmaceutical forms | Powder and solvent for suspension for injection |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: | |
| 0.5 mL, subcutaneous, 1 injection at M0, M0+6 months, and M0+12 months. | |
| Investigational medicinal product name | MMR vaccine (TRIMOVAX®) |
| Investigational medicinal product code | 065 |
| Other name | |
| Pharmaceutical forms | Powder and suspension for suspension for injection |
| Routes of administration | Subcutaneous use |
| Dosage and administration details: | |
| 0.5 mL, subcutaneous use, 1 injection at Month-1. | |
| Investigational medicinal product name | PENTAXIM® |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder and suspension for suspension for injection |
| Routes of administration | Intramuscular use |
| Dosage and administration details: | |
| 0.5 mL, intramuscular use, 1 injection at M0+9 months. | |

| Number of subjects in period 1 | Group 1 | Group 2 | Group 3 |
|---------------------------------------|---------|---------|---------|
| Started | 60 | 30 | 60 |
| Completed | 58 | 30 | 57 |
| Not completed | 2 | 0 | 3 |
| Serious event | 1 | - | - |
| Consent withdrawn by subject | 1 | - | 2 |
| Serious adverse event | - | - | 1 |

| Number of subjects in period 1 | Group 4 |
|---------------------------------------|---------|
| Started | 60 |
| Completed | 60 |
| Not completed | 0 |
| Serious event | - |
| Consent withdrawn by subject | - |
| Serious adverse event | - |

Baseline characteristics

Reporting groups

| | |
|--|---------|
| Reporting group title | Group 1 |
| Reporting group description: | |
| Subjects received a total of 5 injections (Dengue vaccine): First injection - Measles, mumps, rubella (MMR) vaccine (Month-1); Second injection - Dengue vaccine (M0), Third injection - Dengue vaccine (M0+6 months); Fourth injection - Diphtheria, Tetanus, Pertussis, Poliomyelitis, and Hib vaccine (M0+9 months), and Fifth injection - Dengue vaccine (M0+12 months). | |
| Reporting group title | Group 2 |
| Reporting group description: | |
| Subjects received a total of 5 injections (control): First injection - MMR (Month-1); Second injection; control Varicella vaccine (M0); Third injection; control Hepatitis A vaccine (M0 + 6 months); Fourth injection; Diphtheria, Tetanus, Pertussis, Poliomyelitis, and Hib vaccine (M0 + 9 months), and Fifth injection - control Hepatitis A vaccine (M0+12 months). | |
| Reporting group title | Group 3 |
| Reporting group description: | |
| Subjects received a total of 6 injections: First injection - control Varicella vaccine (Month-1); Second Dengue vaccine and third MMR injections (M0); Fourth injection; Dengue vaccine (M0+6 months); Fifth injection - Diphtheria, Tetanus, Pertussis, Poliomyelitis, and Hib vaccine (M0+9 months), and Sixth injection; Dengue vaccine (M0+12 months). | |
| Reporting group title | Group 4 |
| Reporting group description: | |
| Subjects received a total of 6 injections (sequential administration): First injection - MMR (Month-1); Second Dengue vaccine and third placebo injections (M0); Fourth injection - Dengue vaccine (M0+6 months); Fifth injection - Diphtheria, Tetanus, Pertussis, Poliomyelitis, and Hib vaccine (M0+9 months), and Sixth injection - Dengue vaccine (M0+12 months) | |

| Reporting group values | Group 1 | Group 2 | Group 3 |
|--|---------|---------|---------|
| Number of subjects | 60 | 30 | 60 |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 60 | 30 | 60 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Units: months | | | |
| arithmetic mean | 13.4 | 13.3 | 12.7 |
| standard deviation | ± 1.05 | ± 0.969 | ± 0.864 |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 22 | 12 | 26 |
| Male | 38 | 18 | 34 |
| Reporting group values | Group 4 | Total | |

| | | | |
|---|---------|-----|--|
| Number of subjects | 60 | 210 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 60 | 210 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 0 | 0 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Units: months | | | |
| arithmetic mean | 12.8 | | |
| standard deviation | ± 0.971 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Female | 28 | 88 | |
| Male | 32 | 122 | |

End points

End points reporting groups

| | |
|--|---------|
| Reporting group title | Group 1 |
| Reporting group description: | |
| Subjects received a total of 5 injections (Dengue vaccine): First injection - Measles, mumps, rubella (MMR) vaccine (Month-1); Second injection - Dengue vaccine (M0), Third injection - Dengue vaccine (M0+6 months); Fourth injection - Diphtheria, Tetanus, Pertussis, Poliomyelitis, and Hib vaccine (M0+9 months), and Fifth injection - Dengue vaccine (M0+12 months). | |
| Reporting group title | Group 2 |
| Reporting group description: | |
| Subjects received a total of 5 injections (control): First injection - MMR (Month-1); Second injection; control Varicella vaccine (M0); Third injection; control Hepatitis A vaccine (M0 + 6 months); Fourth injection; Diphtheria, Tetanus, Pertussis, Poliomyelitis, and Hib vaccine (M0 + 9 months), and Fifth injection - control Hepatitis A vaccine (M0+12 months). | |
| Reporting group title | Group 3 |
| Reporting group description: | |
| Subjects received a total of 6 injections: First injection - control Varicella vaccine (Month-1); Second Dengue vaccine and third MMR injections (M0); Fourth injection; Dengue vaccine (M0+6 months); Fifth injection - Diphtheria, Tetanus, Pertussis, Poliomyelitis, and Hib vaccine (M0+9 months), and Sixth injection; Dengue vaccine (M0+12 months). | |
| Reporting group title | Group 4 |
| Reporting group description: | |
| Subjects received a total of 6 injections (sequential administration): First injection - MMR (Month-1); Second Dengue vaccine and third placebo injections (M0); Fourth injection - Dengue vaccine (M0+6 months); Fifth injection - Diphtheria, Tetanus, Pertussis, Poliomyelitis, and Hib vaccine (M0+9 months), and Sixth injection - Dengue vaccine (M0+12 months) | |

Primary: Percentage of Subjects Reporting a Solicited Injection-site or Systemic Reactions Following Any Vaccination with Sanofi Pasteur's CYD Dengue Vaccine

| | |
|---|---|
| End point title | Percentage of Subjects Reporting a Solicited Injection-site or Systemic Reactions Following Any Vaccination with Sanofi Pasteur's CYD Dengue Vaccine ^[1] |
| End point description: | |
| Solicited injection site reactions: Pain, Erythema, Swelling. Grade 3 solicited injection site reactions: Pain, Cries when injected limb is moved or the movement of the injected limb is reduced; Erythema and Swelling, ≥ 5 cm. Solicited systemic reactions: Fever, Vomiting, Crying abnormal, Drowsiness, Appetite lost, and Irritability. Grade 3 solicited systemic reactions: Fever, $>39.5^{\circ}\text{C}$ or $>103.1^{\circ}\text{F}$; Vomiting, ≥ 6 episodes per 24 hours or requiring parenteral hydration; Crying abnormal, >3 hours; Drowsiness, Sleeping most of the time or difficult to wake up; Appetite lost, Refused ≥ 3 feeds/meals or refused most feeds/meals; Irritability, Inconsolable. | |
| End point type | Primary |
| End point timeframe: | |
| Day 0 (pre-vaccination) up to Day 7 post-any vaccination | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

| End point values | Group 1 | Group 2 | Group 3 | Group 4 |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 60 | 30 | 59 | 60 |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Injection site Pain | 20 | 20 | 10.2 | 6.7 |
| Grade 3 Injection site Pain | 0 | 0 | 0 | 0 |
| Injection site Erythema | 5 | 16.7 | 11.9 | 3.3 |
| Grade 3 Injection site Erythema | 0 | 0 | 0 | 0 |
| Injection site Swelling | 3.3 | 10 | 1.7 | 1.7 |
| Grade 3 Injection site Swelling | 0 | 0 | 0 | 0 |
| Fever | 26.7 | 36.7 | 42.4 | 25 |
| Grade 3 Fever | 0 | 0 | 0 | 0 |
| Vomiting | 13.3 | 36.7 | 5.1 | 5 |
| Grade 3 Vomiting | 0 | 0 | 0 | 0 |
| Crying abnormal | 23.3 | 26.7 | 13.6 | 11.7 |
| Grade 3 Crying abnormal | 0 | 0 | 0 | 0 |
| Drowsiness | 8.3 | 10 | 3.4 | 5 |
| Grade 3 Drowsiness | 0 | 0 | 0 | 0 |
| Appetite lost | 18.3 | 20 | 11.9 | 10 |
| Grade 3 Appetite lost | 0 | 0 | 0 | 0 |
| Irritability | 31.7 | 36.7 | 11.9 | 20 |
| Grade 3 Irritability | 0 | 0 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Reporting a Solicited Injection-site or Systemic Reactions Following First Vaccination with Sanofi Pasteur's CYD Dengue Vaccine

| | |
|-----------------|---|
| End point title | Percentage of Subjects Reporting a Solicited Injection-site or Systemic Reactions Following First Vaccination with Sanofi Pasteur's CYD Dengue Vaccine ^[2] |
|-----------------|---|

End point description:

Solicited injection site reactions: Pain, Erythema, Swelling. Grade 3 solicited injection site reactions: Pain, Cries when injected limb is moved or the movement of the injected limb is reduced; Erythema and Swelling, ≥5 cm. Solicited systemic reactions: Fever, Vomiting, Crying abnormal, Drowsiness, Appetite lost, and Irritability. Grade 3 solicited systemic reactions: Fever, >39.5°C or >103.1°F; Vomiting, ≥6 episodes per 24 hours or requiring parenteral hydration; Crying abnormal, >3 hours; Drowsiness, Sleeping most of the time or difficult to wake up; Appetite lost, Refused ≥3 feeds/meals or refused most feeds/meals; Irritability, Inconsolable.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Day 0 (pre-vaccination) up to Day 7 post-first vaccination

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

| End point values | Group 1 | Group 2 | Group 3 | Group 4 |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 60 | 30 | 59 | 60 |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Injection site Pain | 13.3 | 20 | 6.8 | 5 |
| Grade 3 Injection site Pain | 0 | 0 | 0 | 0 |
| Injection site Erythema | 5 | 16.7 | 10.2 | 3.3 |
| Grade 3 Injection site Erythema | 0 | 0 | 0 | 0 |
| Injection site Swelling | 3.3 | 10 | 1.7 | 1.7 |
| Grade 3 Injection site Swelling | 0 | 0 | 0 | 0 |
| Fever | 20 | 20 | 28.8 | 11.7 |
| Grade 3 Fever | 0 | 0 | 0 | 0 |
| Vomiting | 11.7 | 30 | 1.7 | 1.7 |
| Grade 3 Vomiting | 0 | 0 | 0 | 0 |
| Crying abnormal | 20 | 23.3 | 13.6 | 10 |
| Grade 3 Crying abnormal | 0 | 0 | 0 | 0 |
| Drowsiness | 6.7 | 10 | 3.4 | 5 |
| Grade 3 Drowsiness | 0 | 0 | 0 | 0 |
| Appetite lost | 16.7 | 16.7 | 11.9 | 5 |
| Grade 3 Appetite lost | 0 | 0 | 0 | 0 |
| Irritability | 26.7 | 33.3 | 11.9 | 18.3 |
| Grade 3 Irritability | 0 | 0 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Reporting a Solicited Injection-site or Systemic Reactions Following Second Vaccination with Sanofi Pasteur's CYD Dengue Vaccine

| | |
|-----------------|--|
| End point title | Percentage of Subjects Reporting a Solicited Injection-site or Systemic Reactions Following Second Vaccination with Sanofi Pasteur's CYD Dengue Vaccine ^[3] |
|-----------------|--|

End point description:

Solicited injection site reactions: Pain, Erythema, Swelling. Grade 3 solicited injection site reactions: Pain, Cries when injected limb is moved or the movement of the injected limb is reduced; Erythema and Swelling, ≥ 5 cm. Solicited systemic reactions: Fever, Vomiting, Crying abnormal, Drowsiness, Appetite lost, and Irritability. Grade 3 solicited systemic reactions: Fever, $>39.5^{\circ}\text{C}$ or $>103.1^{\circ}\text{F}$; Vomiting, ≥ 6 episodes per 24 hours or requiring parenteral hydration; Crying abnormal, >3 hours; Drowsiness, Sleeping most of the time or difficult to wake up; Appetite lost, Refused ≥ 3 feeds/meals or refused most feeds/meals; Irritability, Inconsolable.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Day 0 (pre-vaccination) up to Day 7 post-second vaccination

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

| End point values | Group 1 | Group 2 | Group 3 | Group 4 |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 60 | 30 | 58 | 60 |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Injection site Pain | 5 | 3.3 | 1.7 | 1.7 |
| Grade 3 Injection site Pain | 0 | 0 | 0 | 0 |
| Injection site Erythema | 0 | 3.3 | 1.7 | 0 |
| Grade 3 Injection site Erythema | 0 | 0 | 0 | 0 |
| Injection site Swelling | 0 | 3.3 | 0 | 0 |
| Grade 3 Injection site Swelling | 0 | 0 | 0 | 0 |
| Fever | 3.3 | 10 | 8.6 | 6.7 |
| Grade 3 Fever | 0 | 0 | 0 | 0 |
| Vomiting | 0 | 3.3 | 3.4 | 1.7 |
| Grade 3 Vomiting | 0 | 0 | 0 | 0 |
| Crying abnormal | 0 | 6.7 | 0 | 0 |
| Grade 3 Crying abnormal | 0 | 0 | 0 | 0 |
| Drowsiness | 0 | 0 | 0 | 0 |
| Grade 3 Drowsiness | 0 | 0 | 0 | 0 |
| Appetite lost | 1.7 | 6.7 | 0 | 3.3 |
| Grade 3 Appetite lost | 0 | 0 | 0 | 0 |
| Irritability | 3.3 | 10 | 0 | 1.7 |
| Grade 3 Irritability | 0 | 0 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects Reporting a Solicited Injection-site or Systemic Reactions Following Third Vaccination with Sanofi Pasteur's CYD Dengue Vaccine

| | |
|-----------------|---|
| End point title | Percentage of Subjects Reporting a Solicited Injection-site or Systemic Reactions Following Third Vaccination with Sanofi Pasteur's CYD Dengue Vaccine ^[4] |
|-----------------|---|

End point description:

Solicited injection site reactions: Pain, Erythema, Swelling. Grade 3 solicited injection site reactions: Pain, Cries when injected limb is moved or the movement of the injected limb is reduced; Erythema and Swelling, ≥5 cm. Solicited systemic reactions: Fever, Vomiting, Crying abnormal, Drowsiness, Appetite lost, and Irritability. Grade 3 solicited systemic reactions: Fever, >39.5°C or >103.1°F; Vomiting, ≥6 episodes per 24 hours or requiring parenteral hydration; Crying abnormal, >3 hours; Drowsiness, Sleeping most of the time or difficult to wake up; Appetite lost, Refused ≥3 feeds/meals or refused most feeds/meals; Irritability, Inconsolable.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Day 0 (pre-vaccination) up to Day 7 post-third vaccination

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

| End point values | Group 1 | Group 2 | Group 3 | Group 4 |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 58 | 30 | 57 | 60 |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Injection site Pain | 3.4 | 0 | 1.8 | 0 |
| Grade 3 Injection site Pain | 0 | 0 | 0 | 0 |
| Injection site Erythema | 0 | 3.3 | 0 | 0 |
| Grade 3 Injection site Erythema | 0 | 0 | 0 | 0 |
| Injection site Swelling | 0 | 0 | 0 | 0 |
| Grade 3 Injection site Swelling | 0 | 0 | 0 | 0 |
| Fever | 10.3 | 6.7 | 8.8 | 8.3 |
| Grade 3 Fever | 0 | 0 | 0 | 0 |
| Vomiting | 1.7 | 3.3 | 0 | 1.7 |
| Grade 3 Vomiting | 0 | 0 | 0 | 0 |
| Crying abnormal | 3.4 | 0 | 0 | 1.7 |
| Grade 3 Crying abnormal | 0 | 0 | 0 | 0 |
| Drowsiness | 1.7 | 0 | 0 | 0 |
| Grade 3 Drowsiness | 0 | 0 | 0 | 0 |
| Appetite lost | 1.7 | 0 | 0 | 3.3 |
| Grade 3 Appetite lost | 0 | 0 | 0 | 0 |
| Irritability | 3.4 | 3.3 | 0 | 3.3 |
| Grade 3 Irritability | 0 | 0 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects with Non-serotype Specific CYD Viremia after the First Vaccination with Sanofi Pasteur's CYD Dengue Vaccine

| | |
|-----------------|---|
| End point title | Percentage of Subjects with Non-serotype Specific CYD Viremia after the First Vaccination with Sanofi Pasteur's CYD Dengue Vaccine ^[5] |
|-----------------|---|

End point description:

Non-specific specific CYD viremia was assessed using yellow fever (YF) real time polymerase chain reaction (RT-PCR).

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Day 0 (pre-vaccination) up to Day 8 (post-first vaccination)

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

| End point values | Group 1 | Group 2 | Group 3 | Group 4 |
|-------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 60 | 30 | 57 | 60 |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Viremia detectable | 48.3 | 0 | 17.5 | 28.3 |
| Viremia quantified | 1.7 | 0 | 1.8 | 1.7 |

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects with Seropositivity for Parental Dengue Virus Serotypes Following Each Vaccination with Sanofi Pasteur's CYD Dengue Vaccine

| | |
|-----------------|---|
| End point title | Percentage of Subjects with Seropositivity for Parental Dengue Virus Serotypes Following Each Vaccination with Sanofi Pasteur's CYD Dengue Vaccine ^[6] |
|-----------------|---|

End point description:

Neutralizing antibody levels against each of the 4 parental dengue virus serotype strains were measured using the dengue neutralization assay. Seropositivity was defined as subjects with antibody titers ≥ 10 1/dil against the 4 dengue serotypes.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Day 0 (pre-vaccination) and Day 28 post-second and third injections for Groups 1 and 2 and post-first, second, and third injections for Groups 3 and 4.

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

| End point values | Group 1 | Group 2 | Group 3 | Group 4 |
|--|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 60 | 30 | 58 | 60 |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| Dengue Parental Serotype 1; Pre-inj. 1 (Screening) | 10 | 3.3 | 6.9 | 10 |
| Dengue Parental Serotype 1; Post-inj. 1 (V04) | 0 | 0 | 19 | 30 |
| Dengue Parental Serotype 1; Post-inj. 2 (V07) | 91.5 | 23.3 | 87.9 | 93.3 |
| Dengue Parental Serotype 1; Post-inj. 1 (V10) | 94.8 | 20 | 94.7 | 96.7 |
| Dengue Parental Serotype 2; Pre-inj. 1 (Screening) | 18.3 | 16.7 | 13.8 | 10 |
| Dengue Parental Serotype 2; Post-inj. 1 (V04) | 0 | 0 | 29.3 | 33.3 |
| Dengue Parental Serotype 2; Post-inj. 2 (V07) | 94.9 | 26.7 | 94.8 | 98.3 |
| Dengue Parental Serotype 2; Post-inj. 3 (V10) | 96.6 | 33.3 | 96.5 | 100 |
| Dengue Parental Serotype 3; Pre-inj. 1 (Screening) | 26.7 | 23.3 | 37.9 | 40.7 |

| | | | | |
|--|------|------|------|------|
| Dengue Parental Serotype 3; Post-inj. 1 (V04) | 0 | 0 | 70.7 | 86.7 |
| Dengue Parental Serotype 3; Post-inj. 2 (V07) | 100 | 40 | 100 | 98.3 |
| Dengue Parental Serotype 3; Post-inj. 3 (V10) | 100 | 36.7 | 100 | 100 |
| Dengue Parental Serotype 4; Pre-inj. 1 (Screening) | 25 | 21.4 | 5.2 | 16.7 |
| Dengue Parental Serotype 4; Post-inj. 1 (V04) | 0 | 0 | 53.4 | 83.3 |
| Dengue Parental Serotype 4; Post-inj. 2 (V07) | 100 | 40 | 96.6 | 98.3 |
| Dengue Parental Serotype 4; Post-inj. 3 (V10) | 98.3 | 23.3 | 96.5 | 100 |

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Subjects with Seropositivity for at Least 1, 2, 3 or 4 Parental Dengue Virus Serotypes Before and After Each Vaccination with Sanofi Pasteur's CYD Dengue Vaccine

| | |
|-----------------|--|
| End point title | Percentage of Subjects with Seropositivity for at Least 1, 2, 3 or 4 Parental Dengue Virus Serotypes Before and After Each Vaccination with Sanofi Pasteur's CYD Dengue Vaccine ^[7] |
|-----------------|--|

End point description:

Neutralizing antibody levels of at least 1, 2, 3 or the 4 parental dengue virus serotype strains were measured using the dengue neutralization assay. Seropositivity was defined as subjects with antibody titers ≥ 10 1/dil against the 4 dengue serotypes.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Day 0 (pre-vaccination) and Day 28 post-second and third injections for Groups 1 and 2 and post-first, second, and third injections for Groups 3 and 4.

Notes:

[7] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

| End point values | Group 1 | Group 2 | Group 3 | Group 4 |
|--|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 60 | 30 | 58 | 60 |
| Units: Percentage of subjects | | | | |
| number (not applicable) | | | | |
| At least 1 serotype; Pre-inj. 1 (Screening) | 38.3 | 43.3 | 46.6 | 46.7 |
| At least 1 serotype; Post-inj. 1 (V04) | 0 | 0 | 82.8 | 91.7 |
| At least 1 serotype; Post-inj. 2 (V07) | 100 | 50 | 100 | 100 |
| At least 1 serotype; Post-inj. 3 (V10) | 100 | 43.3 | 100 | 100 |
| At least 2 serotypes; Pre-inj. 1 (Screening) | 21.7 | 13.3 | 12.1 | 15 |
| At least 2 serotypes; Post-inj. 1 (V04) | 0 | 0 | 53.4 | 81.7 |
| At least 2 serotypes; Post-inj. 2 (V07) | 100 | 36.7 | 98.3 | 100 |
| At least 2 serotypes; Post-inj. 3 (V10) | 100 | 30 | 100 | 100 |

| | | | | |
|--|------|------|------|------|
| At least 3 serotypes; Pre-inj. 1 (Screening) | 11.7 | 3.3 | 3.4 | 8.3 |
| At least 3 serotypes; Post-inj. 1 (V04) | 0 | 0 | 24.1 | 38.3 |
| At least 3 serotypes; Post-inj. 2 (V07) | 94.9 | 23.3 | 93.1 | 98.3 |
| At least 3 serotypes; Post-inj. 3 (V10) | 96.6 | 26.7 | 96.5 | 100 |
| 4 serotypes; Pre-inj. 1 (Screening) | 8.3 | 3.3 | 1.7 | 6.7 |
| 4 serotypes; Post-inj. 1 (V04) | 0 | 0 | 12.1 | 21.7 |
| 4 serotypes; Post-inj. 2 (V07) | 91.5 | 20 | 87.9 | 90 |
| 4 serotypes; Post-inj. 3 (V10) | 93.1 | 13.3 | 91.2 | 96.7 |

Statistical analyses

No statistical analyses for this end point

Primary: Geometric Mean Titers (GMTs) of Antibodies Against Each Parental Dengue Virus Serotype Before and Following Each Vaccination with Sanofi Pasteur's CYD Dengue Vaccine

| | |
|-----------------|--|
| End point title | Geometric Mean Titers (GMTs) of Antibodies Against Each Parental Dengue Virus Serotype Before and Following Each Vaccination with Sanofi Pasteur's CYD Dengue Vaccine ^[8] |
|-----------------|--|

End point description:

Geometric mean titers of antibodies against parental dengue virus serotypes were measured using the dengue neutralization assay.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Day 0 (pre-vaccination) and Day 28 post-second and third injections for Groups 1 and 2 and post-first, second, and third injections for Groups 3 and 4.

Notes:

[8] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Descriptive analyses were performed based on the study groups and the study vaccine administered for this outcome.

| End point values | Group 1 | Group 2 | Group 3 | Group 4 |
|--|---------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 60 | 30 | 58 | 60 |
| Units: Titers (1/dil) | | | | |
| geometric mean (confidence interval 95%) | | | | |
| Dengue Parental Serotype 1; Pre-inj. 1 (Screening) | 6.39 (5.21 to 7.85) | 5.31 (4.69 to 6.02) | 5.59 (4.94 to 6.33) | 6.18 (5.16 to 7.41) |
| Dengue Parental Serotype 1; Post-inj. 1 (V04) | 0 (0 to 0) | 0 (0 to 0) | 7.36 (5.9 to 9.18) | 10.4 (7.33 to 14.8) |
| Dengue Parental Serotype 1; Post-inj. 2 (V07) | 69.8 (45.4 to 108) | 9.04 (5.59 to 14.6) | 62.5 (43.8 to 89.1) | 73 (51.4 to 104) |
| Dengue Parental Serotype 1; Post-inj. 3 (V10) | 105 (73.8 to 148) | 11.5 (5.77 to 22.8) | 108 (80.7 to 144) | 124 (90.9 to 169) |
| Dengue Parental Serotype 2; Pre-inj. 1 (Screening) | 10 (6.54 to 15.4) | 9.73 (5.18 to 18.3) | 7.2 (5.3 to 9.77) | 7.46 (5.25 to 10.6) |
| Dengue Parental Serotype 2; Post-inj. 1 (V04) | 0 (0 to 0) | 0 (0 to 0) | 10.6 (7.29 to 15.6) | 14.8 (9.26 to 23.7) |
| Dengue Parental Serotype 2; Post-inj. 2 (V07) | 159 (93.1 to 272) | 14.5 (6.81 to 30.8) | 141 (88.7 to 224) | 114 (76.5 to 168) |
| Dengue Parental Serotype 2; Post-inj. 3 (V10) | 147 (99.2 to 219) | 15.7 (7.7 to 32) | 213 (146 to 311) | 176 (121 to 254) |

| | | | | |
|--|---------------------|---------------------|---------------------|---------------------|
| Dengue Parental Serotype 3; Pre-inj. 1 (Screening) | 10.1 (6.99 to 14.5) | 9.05 (5.8 to 14.1) | 13.8 (9.49 to 20) | 14.8 (9.5 to 23.1) |
| Dengue Parental Serotype 3; Post-inj. 1 (V04) | 0 (0 to 0) | 0 (0 to 0) | 30.8 (21 to 45.1) | 96 (61.9 to 149) |
| Dengue Parental Serotype 3; Post-inj. 2 (V07) | 249 (170 to 366) | 13.9 (8.1 to 23.8) | 254 (196 to 329) | 288 (197 to 420) |
| Dengue Parental Serotype 3; Post-inj. 3 (V10) | 311 (222 to 436) | 13.4 (7.63 to 23.5) | 358 (277 to 464) | 387 (284 to 527) |
| Dengue Parental Serotype 4; Pre-inj. 1 (Screening) | 8.25 (6.4 to 10.7) | 6.98 (5.41 to 9.01) | 5.6 (4.9 to 6.4) | 6.99 (5.66 to 8.63) |
| Dengue Parental Serotype 4; Post-inj. 1 (V04) | 0 (0 to 0) | 0 (0 to 0) | 20.5 (13.7 to 30.5) | 89.1 (56.8 to 140) |
| Dengue Parental Serotype 4; Post-inj. 2 (V07) | 131 (104 to 166) | 10.1 (7.14 to 14.2) | 121 (90.7 to 161) | 133 (100 to 176) |
| Dengue Parental Serotype 4; Post-inj. 3 (V10) | 143 (107 to 192) | 8.16 (5.66 to 11.8) | 127 (96 to 169) | 160 (131 to 195) |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event data were collected from Day 0 (post-vaccination) up to Day 28 post-each vaccination.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 12.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|---------|
| Reporting group title | Group 1 |
|-----------------------|---------|

Reporting group description:

Toddlers who received at total of 5 injections (Dengue vaccine): Month-1 (first injection; MMR), M0 (second injection; Dengue vaccine), M0+6 months (third injection; Dengue vaccine), M0+9 months (fourth injection; Diphtheria, Tetanus, Pertussis, Poliomyelitis, and Hib vaccine), and M0+12 months (fifth injection; Dengue vaccine).

| | |
|-----------------------|---------|
| Reporting group title | Group 2 |
|-----------------------|---------|

Reporting group description:

Toddlers who received at total of 5 injections (control): Month-1 (first injection; MMR), M0 (second injection; control Varicella vaccine), M0+6 months (third injection; control Hepatitis A vaccine), M0+9 months (fourth injection; Diphtheria, Tetanus, Pertussis, Poliomyelitis, and Hib vaccine), and M0+12 months (fifth injection; control Hepatitis A vaccine).

| | |
|-----------------------|---------|
| Reporting group title | Group 3 |
|-----------------------|---------|

Reporting group description:

Toddlers who received a total of 6 injections: Month-1 (first injection; control Varicella vaccine), M0 (second [Dengue vaccine] and third [MMR] injections), M0+6 months (fourth injection; Dengue vaccine), M0+9 months (fifth injection; Diphtheria, Tetanus, Pertussis, Poliomyelitis, and Hib vaccine), and M0+12 months (sixth injection; Dengue vaccine).

| | |
|-----------------------|---------|
| Reporting group title | Group 4 |
|-----------------------|---------|

Reporting group description:

Toddlers who received a total of 6 injections (sequential administration): Month-1 (first injection; MMR), M0 (second [Dengue vaccine] and third [placebo] injections), M0+6 months (fourth injection; Dengue vaccine), M0+9 months (fifth injection; Diphtheria, Tetanus, Pertussis, Poliomyelitis, and Hib vaccine), and M0+12 months (sixth injection; Dengue vaccine).

| Serious adverse events | Group 1 | Group 2 | Group 3 |
|---|----------------|----------------|-----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 1 / 30 (3.33%) | 7 / 59 (11.86%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Nervous system disorders | | | |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | 0 / 30 (0.00%) | 0 / 59 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile convulsion | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 30 (0.00%) | 3 / 59 (5.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Nephrotic syndrome | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 30 (0.00%) | 0 / 59 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Dengue fever | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 30 (0.00%) | 1 / 59 (1.69%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 0 / 30 (0.00%) | 3 / 59 (5.08%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | 1 / 30 (3.33%) | 2 / 59 (3.39%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|--|--|
| Serious adverse events | Group 4 | | |
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Nervous system disorders | | | |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Febrile convulsion | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Nephrotic syndrome | | | |
| subjects affected / exposed | 1 / 60 (1.67%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Dengue fever | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 0 / 60 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 5 %

| Non-serious adverse events | Group 1 | Group 2 | Group 3 |
|---|------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 24 / 60 (40.00%) | 15 / 30 (50.00%) | 25 / 59 (42.37%) |
| Nervous system disorders | | | |
| Drowsiness (Post-any injection) | | | |
| alternative assessment type: Systematic | | | |
| subjects affected / exposed | 5 / 60 (8.33%) | 3 / 30 (10.00%) | 2 / 59 (3.39%) |
| occurrences (all) | 5 | 3 | 2 |
| General disorders and administration site conditions | | | |

| | | | |
|--|------------------------|------------------------|------------------------|
| Injection site Pain (Post-any injection) alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 12 / 60 (20.00%) 13 | 6 / 30 (20.00%) 7 | 6 / 59 (10.17%) 10 |
| Injection site Erythema (Post-any injection) alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 3 | 5 / 30 (16.67%) 7 | 7 / 59 (11.86%) 10 |
| Injection site Swelling (Post-any injection) alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 2 / 60 (3.33%) 2 | 3 / 30 (10.00%) 4 | 1 / 59 (1.69%) 1 |
| Fever (Post-any injection) alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 16 / 60 (26.67%) 20 | 11 / 30 (36.67%) 11 | 25 / 59 (42.37%) 27 |
| Gastrointestinal disorders Vomiting (Post-any injection) alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 8 / 60 (13.33%) 8 | 11 / 30 (36.67%) 11 | 3 / 59 (5.08%) 3 |
| Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all) | 1 / 60 (1.67%) 1 | 0 / 30 (0.00%) 0 | 0 / 59 (0.00%) 0 |
| Psychiatric disorders Crying abnormal (Post-any injection) alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 14 / 60 (23.33%) 14 | 8 / 30 (26.67%) 9 | 8 / 59 (13.56%) 8 |
| Irritability (Post-any injection) alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 19 / 60 (31.67%) 20 | 11 / 30 (36.67%) 14 | 7 / 59 (11.86%) 7 |

| | | | |
|--|------------------------|------------------------|------------------------|
| Infections and infestations Gastroenteritis subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 3 | 2 / 30 (6.67%) 2 | 3 / 59 (5.08%) 3 |
| Rhinitis subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 3 / 30 (10.00%) 3 | 6 / 59 (10.17%) 6 |
| Subcutaneous abscess subjects affected / exposed occurrences (all) | 0 / 60 (0.00%) 0 | 2 / 30 (6.67%) 2 | 1 / 59 (1.69%) 1 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 24 / 60 (40.00%) 30 | 15 / 30 (50.00%) 20 | 19 / 59 (32.20%) 20 |
| Viral infection subjects affected / exposed occurrences (all) | 9 / 60 (15.00%) 10 | 1 / 30 (3.33%) 1 | 11 / 59 (18.64%) 13 |
| Viral rhinitis subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 3 | 5 / 30 (16.67%) 5 | 0 / 59 (0.00%) 0 |
| Viral upper respiratory tract infection subjects affected / exposed occurrences (all) | 4 / 60 (6.67%) 4 | 4 / 30 (13.33%) 4 | 0 / 59 (0.00%) 0 |
| Metabolism and nutrition disorders Appetite lost (Post-any injection) alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 11 / 60 (18.33%) 12 | 6 / 30 (20.00%) 7 | 7 / 59 (11.86%) 7 |

| | | | |
|---|---------------------|--|--|
| Non-serious adverse events | Group 4 | | |
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 17 / 60 (28.33%) | | |
| Nervous system disorders Drowsiness (Post-any injection) alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 3 | | |
| General disorders and administration site conditions | | | |

| | | | |
|--|------------------------|--|--|
| Injection site Pain (Post-any injection) alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 4 / 60 (6.67%) 7 | | |
| Injection site Erythema (Post-any injection) alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 2 / 60 (3.33%) 3 | | |
| Injection site Swelling (Post-any injection) alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 1 / 60 (1.67%) 1 | | |
| Fever (Post-any injection) alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 15 / 60 (25.00%) 16 | | |
| Gastrointestinal disorders Vomiting (Post-any injection) alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 3 | | |
| Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all) | 3 / 60 (5.00%) 4 | | |
| Psychiatric disorders Crying abnormal (Post-any injection) alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 7 / 60 (11.67%) 7 | | |
| Irritability (Post-any injection) alternative assessment type: Systematic subjects affected / exposed occurrences (all) | 12 / 60 (20.00%) 14 | | |

| | | | |
|---|--|--|--|
| <p>Infections and infestations</p> <p>Gastroenteritis</p> <p>subjects affected / exposed</p> <p>0 / 60 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Rhinitis</p> <p>subjects affected / exposed</p> <p>1 / 60 (1.67%)</p> <p>occurrences (all)</p> <p>1</p> <p>Subcutaneous abscess</p> <p>subjects affected / exposed</p> <p>1 / 60 (1.67%)</p> <p>occurrences (all)</p> <p>1</p> <p>Upper respiratory tract infection</p> <p>subjects affected / exposed</p> <p>17 / 60 (28.33%)</p> <p>occurrences (all)</p> <p>18</p> <p>Viral infection</p> <p>subjects affected / exposed</p> <p>6 / 60 (10.00%)</p> <p>occurrences (all)</p> <p>6</p> <p>Viral rhinitis</p> <p>subjects affected / exposed</p> <p>0 / 60 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> <p>Viral upper respiratory tract infection</p> <p>subjects affected / exposed</p> <p>0 / 60 (0.00%)</p> <p>occurrences (all)</p> <p>0</p> | | | |
| <p>Metabolism and nutrition disorders</p> <p>Appetite lost (Post-any injection)</p> <p>alternative assessment type:</p> <p>Systematic</p> <p>subjects affected / exposed</p> <p>6 / 60 (10.00%)</p> <p>occurrences (all)</p> <p>7</p> | | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 12 February 2010 | Administrative edits to revise and update - "Observational" Objectives or Endpoints; definition of a febrile episode; detection of symptomatic dengue cases for homogeneity in the protocol; the time window for the M15 phone call/home visit; and the addition that a "convalescent sample" of 2 mL would be taken in case of suspected symptomatic dengue cases to investigate the relationship between dengue and injection. Other revisions include - statement of applicable exclusion criteria; assessment of febrile convulsions according to the Guideline for definition and collection of cases of febrile convulsions; clarification that toddlers with abnormal biological parameters would be followed up until parameters returned to normal ranges; Specification that wild-type (WT) dengue RT-PCR was tested in acute samples collected from suspected dengue cases, regardless of time of event after injection; and modified the "Interpretation of Results" section. |
| 09 April 2010 | Revised study design from a monocenter to multi-center in view of measles outbreak in the Philippines; Acceleration of recruitment rate for Cohort 3 for protection against measles at the earliest possible time; Revision of "Visit Procedures" to notify general practitioners that patients were going to receive MMR injection during the dengue vaccine trial and for Groups 3 and 4. Revision of dengue microneutralization assay to dengue neutralization assay; Pan flavivirus reverse transcriptase polymerase chain reaction (RT-PCR) was changed to dengue screen RT-PCR and the description of the method was adapted in accordance to the changes. |
| 03 February 2011 | The lower limit of the normal range for Hemoglobin (Hb) was changed from 10.9 g/dL to 9.9 g/dL and the analysis of secondary objectives on measles, mumps, rubella (MMR) vaccine was revised. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported