



## Clinical trial results:

### Efficacy and Safety of a Novel Tetravalent Dengue Vaccine in Healthy Children Aged 2 to 14 Years in Asia

#### Summary

|                          |                  |
|--------------------------|------------------|
| EudraCT number           | 2014-001708-24   |
| Trial protocol           | Outside EU/EEA   |
| Global end of trial date | 21 November 2017 |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v2 (current)     |
| This version publication date  | 07 December 2018 |
| First version publication date | 17 April 2015    |
| Version creation reason        |                  |

#### Trial information

##### Trial identification

|                       |       |
|-----------------------|-------|
| Sponsor protocol code | CYD14 |
|-----------------------|-------|

##### Additional study identifiers

|                                    |                 |
|------------------------------------|-----------------|
| ISRCTN number                      | -               |
| ClinicalTrials.gov id (NCT number) | NCT01373281     |
| WHO universal trial number (UTN)   | U1111-1116-4957 |

Notes:

#### Sponsors

|                              |                                                                |
|------------------------------|----------------------------------------------------------------|
| Sponsor organisation name    | Sanofi Pasteur                                                 |
| Sponsor organisation address | 14 Espace Henry Vallée, Lyon, France, 69007                    |
| Public contact               | Trial Transparency Team, Sanofi Pasteur, Contact-US@sanofi.com |
| Scientific contact           | Trial Transparency Team, Sanofi Pasteur, Contact-US@sanofi.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                       | 11 July 2018     |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 21 November 2017 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

Efficacy of CYD dengue vaccine after 3 vaccinations at 0, 6 and 12 months in preventing symptomatic virologically-confirmed dengue cases, regardless of the severity, due to any of the four serotypes in children aged 2 to 14 years at the time of inclusion.

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 equipments were 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                          | 03 June 2011     |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety, Efficacy |
| Long term follow-up duration                              | 4 Years          |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Philippines: 3501 |
| Country: Number of subjects enrolled | Malaysia: 1401    |
| Country: Number of subjects enrolled | Vietnam: 2333     |
| Country: Number of subjects enrolled | Thailand: 1170    |
| Country: Number of subjects enrolled | Indonesia: 1870   |
| Worldwide total number of subjects   | 10275             |
| EEA total number of subjects         | 0                 |

Notes:

### Subjects enrolled per age group

|                                        |   |
|----------------------------------------|---|
| In utero                               | 0 |
| Preterm newborn - gestational age < 37 | 0 |

|                                          |      |
|------------------------------------------|------|
| wk                                       |      |
| Newborns (0-27 days)                     | 0    |
| Infants and toddlers (28 days-23 months) | 0    |
| Children (2-11 years)                    | 7946 |
| Adolescents (12-17 years)                | 2329 |
| 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 03 June 2011 to 01 December 2011 at 9 sites in Indonesia, 5 in Malaysia, 3 in Thailand, 5 in Philippines, and 2 in Vietnam.

### Pre-assignment

Screening details:

A total of 10275 subjects were enrolled; all but one met all of the inclusion criteria and none of the exclusion criteria. Three subjects were not vaccinated and were excluded from the Full Analysis Set for Efficacy and the Safety Analysis Set.

### Period 1

|                              |                                          |
|------------------------------|------------------------------------------|
| Period 1 title               | Vaccination Phase (up to 25 Months)      |
| Is this the baseline period? | Yes                                      |
| Allocation method            | Randomised - controlled                  |
| Blinding used                | Double blind                             |
| Roles blinded                | Subject, Investigator, Monitor, Assessor |

Blinding implementation details:

An observer-blind procedure was followed for the 3 CYD dengue vaccine or placebo injections. The 'vaccinator' in charge of preparing and administering the vaccines was not authorized to collect safety data and also ensured that the documents on randomization were stored in a secure place with no unauthorized access.

### Arms

|                              |                          |
|------------------------------|--------------------------|
| Are arms mutually exclusive? | Yes                      |
| <b>Arm title</b>             | CYD Dengue Vaccine Group |

Arm description:

Subjects received 3 doses of CYD dengue vaccine; one each at 0, 6, and 12 months and were followed up to 60 months after last vaccination (for a total duration of up to 72 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, 3 doses at 0, 6, and 12 months.

|                  |               |
|------------------|---------------|
| <b>Arm title</b> | Placebo Group |
|------------------|---------------|

Arm description:

Subjects received 3 doses of placebo matched to vaccine; one each at 0, 6, and 12 months and were followed up to 60 months after last vaccination (for a total duration of up to 72 months).

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Placebo                |
| Investigational medicinal product name | Placebo (NaCl)         |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

Dosage and administration details:

0.5 mL, subcutaneous, 3 doses at 0, 6, and 12 months.

| Number of subjects in period 1 | CYD Dengue Vaccine Group | Placebo Group |
|--------------------------------|--------------------------|---------------|
| Started                        | 6851                     | 3424          |
| Completed                      | 6797                     | 3397          |
| Not completed                  | 54                       | 27            |
| Consent withdrawn by subject   | 40                       | 23            |
| Serious adverse event          | 4                        | 1             |
| Lost to follow-up              | 5                        | 1             |
| Protocol deviation             | 5                        | 2             |

## Period 2

|                              |                                          |
|------------------------------|------------------------------------------|
| Period 2 title               | Surveillance Expansion Period            |
| Is this the baseline period? | No                                       |
| Allocation method            | Randomised - controlled                  |
| Blinding used                | Double blind                             |
| Roles blinded                | Subject, Investigator, Monitor, Assessor |

Blinding implementation details:

An observer-blind procedure was followed for the 3 CYD dengue vaccine or placebo injections. The 'vaccinator' in charge of preparing and administering the vaccines was not authorized to collect safety data and also ensured that the documents on randomization were stored in a secure place with no unauthorized access

## Arms

|                              |                          |
|------------------------------|--------------------------|
| Are arms mutually exclusive? | Yes                      |
| <b>Arm title</b>             | CYD Dengue Vaccine Group |

Arm description:

Subjects received 3 doses of CYD dengue vaccine; one each at 0, 6, and 12 months and were followed up to 60 months after last vaccination (for a total duration of up to 72 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, 3 doses at 0, 6, and 12 months.

|                  |               |
|------------------|---------------|
| <b>Arm title</b> | Placebo Group |
|------------------|---------------|

Arm description:

Subjects received 3 doses of placebo matched to vaccine; one each at 0, 6, and 12 months and were followed up to 60 months after last vaccination (for a total duration of up to 72 months).

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Placebo                |
| Investigational medicinal product name | Placebo (NaCl)         |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Solution for injection |
| Routes of administration               | Subcutaneous use       |

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Dosage and administration details:

0.5 mL, subcutaneous, 3 doses at 0, 6, and 12 months.

| <b>Number of subjects in period 2</b> | CYD Dengue Vaccine Group | Placebo Group |
|---------------------------------------|--------------------------|---------------|
| Started                               | 6797                     | 3397          |
| Completed                             | 6595                     | 3279          |
| Not completed                         | 202                      | 118           |
| Consent withdrawn by subject          | 180                      | 105           |
| Serious adverse event                 | 3                        | 4             |
| Lost to follow-up                     | 10                       | 8             |
| Protocol deviation                    | 9                        | 1             |

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                              |                          |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|
| Reporting group title                                                                                                                                                                        | CYD Dengue Vaccine Group |
| Reporting group description:                                                                                                                                                                 |                          |
| Subjects received 3 doses of CYD dengue vaccine; one each at 0, 6, and 12 months and were followed up to 60 months after last vaccination (for a total duration of up to 72 months).         |                          |
| Reporting group title                                                                                                                                                                        | Placebo Group            |
| Reporting group description:                                                                                                                                                                 |                          |
| Subjects received 3 doses of placebo matched to vaccine; one each at 0, 6, and 12 months and were followed up to 60 months after last vaccination (for a total duration of up to 72 months). |                          |

| Reporting group values                             | CYD Dengue Vaccine Group | Placebo Group | Total |
|----------------------------------------------------|--------------------------|---------------|-------|
| Number of subjects                                 | 6851                     | 3424          | 10275 |
| 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)           | 0                        | 0             | 0     |
| Children (2-11 years)                              | 5296                     | 2650          | 7946  |
| Adolescents (12-17 years)                          | 1555                     | 774           | 2329  |
| Adults (18-64 years)                               | 0                        | 0             | 0     |
| From 65-84 years                                   | 0                        | 0             | 0     |
| 85 years and over                                  | 0                        | 0             | 0     |
| Age continuous                                     |                          |               |       |
| Units: years                                       |                          |               |       |
| arithmetic mean                                    | 8.8                      | 8.8           |       |
| standard deviation                                 | ± 3.45                   | ± 3.42        | -     |
| Gender categorical                                 |                          |               |       |
| Units: Subjects                                    |                          |               |       |
| Female                                             | 3524                     | 1767          | 5291  |
| Male                                               | 3327                     | 1657          | 4984  |

## End points

### End points reporting groups

|                                                                                                                                                                                                                              |                          |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------|
| Reporting group title                                                                                                                                                                                                        | CYD Dengue Vaccine Group |
| Reporting group description:<br>Subjects received 3 doses of CYD dengue vaccine; one each at 0, 6, and 12 months and were followed up to 60 months after last vaccination (for a total duration of up to 72 months).         |                          |
| Reporting group title                                                                                                                                                                                                        | Placebo Group            |
| Reporting group description:<br>Subjects received 3 doses of placebo matched to vaccine; one each at 0, 6, and 12 months and were followed up to 60 months after last vaccination (for a total duration of up to 72 months). |                          |
| Reporting group title                                                                                                                                                                                                        | CYD Dengue Vaccine Group |
| Reporting group description:<br>Subjects received 3 doses of CYD dengue vaccine; one each at 0, 6, and 12 months and were followed up to 60 months after last vaccination (for a total duration of up to 72 months).         |                          |
| Reporting group title                                                                                                                                                                                                        | Placebo Group            |
| Reporting group description:<br>Subjects received 3 doses of placebo matched to vaccine; one each at 0, 6, and 12 months and were followed up to 60 months after last vaccination (for a total duration of up to 72 months). |                          |

### Primary: Number of Symptomatic Virologically Confirmed Dengue (VCD) Cases Due to Any Serotype During the Active Phase Post-Dose 3 Following Injection (Inj.) With Either CYD Dengue Vaccine or a Placebo

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |                                                                                                                                                                                                 |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             | Number of Symptomatic Virologically Confirmed Dengue (VCD) Cases Due to Any Serotype During the Active Phase Post-Dose 3 Following Injection (Inj.) With Either CYD Dengue Vaccine or a Placebo |
| End point description:<br>Symptomatic VCD cases were defined as occurrence of acute febrile illness (temperature $\geq 38^{\circ}\text{C}$ on at least 2 consecutive days) and confirmation of dengue virus infection by dengue reverse transcriptase polymerase chain reaction (RT-PCR) and/or dengue non-structural protein (NS) 1 antigen enzyme-linked immunosorbent assay (ELISA). Vaccine efficacy was defined as 1 minus the ratio of density incidence due to any serotype after at least 1 dose in the CYD Dengue Vaccine Group over the density incidence of the Placebo Vaccine Group. Number of symptomatic VCD cases were assessed in the Per-Protocol Analysis Set for Efficacy which included subjects who did not meet at least one of the protocol-specified inclusion/exclusion criteria. |                                                                                                                                                                                                 |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              | Primary                                                                                                                                                                                         |
| End point timeframe:<br>28 days post-dose 3 and up to 13 months post-dose 3                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                 |

| End point values                                 | CYD Dengue Vaccine Group | Placebo Group   |  |  |
|--------------------------------------------------|--------------------------|-----------------|--|--|
| Subject group type                               | Reporting group          | Reporting group |  |  |
| Number of subjects analysed                      | 6709                     | 3350            |  |  |
| Units: Cases                                     |                          |                 |  |  |
| number (not applicable)                          |                          |                 |  |  |
| Symptomatic virologically-confirmed dengue cases | 117                      | 133             |  |  |



## Statistical analyses

|                                                                                                                                                                                                                                                                                                                                                                                                                                                      |                                            |
|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------|
| <b>Statistical analysis title</b>                                                                                                                                                                                                                                                                                                                                                                                                                    | Vaccine efficacy of the CYD dengue vaccine |
| Statistical analysis description:<br>The statistical methodology was based on the use of the two-sided 95% confidence interval (CI) of the vaccine efficacy (expressed in %). The CI was calculated using the exact method conditional on the total number of cases in both groups (exact method by Breslow & Day). The vaccine efficacy of the CYD dengue vaccine was considered significant if the lower bound of its 95% CI was greater than 25%. |                                            |
| Comparison groups                                                                                                                                                                                                                                                                                                                                                                                                                                    | CYD Dengue Vaccine Group v Placebo Group   |
| Number of subjects included in analysis                                                                                                                                                                                                                                                                                                                                                                                                              | 10059                                      |
| Analysis specification                                                                                                                                                                                                                                                                                                                                                                                                                               | Pre-specified                              |
| Analysis type                                                                                                                                                                                                                                                                                                                                                                                                                                        | other                                      |
| Parameter estimate                                                                                                                                                                                                                                                                                                                                                                                                                                   | Vaccine efficacy (%)                       |
| Point estimate                                                                                                                                                                                                                                                                                                                                                                                                                                       | 56.5                                       |
| Confidence interval                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                            |
| level                                                                                                                                                                                                                                                                                                                                                                                                                                                | 95 %                                       |
| sides                                                                                                                                                                                                                                                                                                                                                                                                                                                | 2-sided                                    |
| lower limit                                                                                                                                                                                                                                                                                                                                                                                                                                          | 43.8                                       |
| upper limit                                                                                                                                                                                                                                                                                                                                                                                                                                          | 66.4                                       |

## Secondary: Geometric Mean Titers of Antibodies Against Each Serotype With the Parental Dengue Virus Strain Before and Following Inj. With Either CYD Dengue Tetravalent Vaccine or a Placebo

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |                                                                                                                                                                                   |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                | Geometric Mean Titers of Antibodies Against Each Serotype With the Parental Dengue Virus Strain Before and Following Inj. With Either CYD Dengue Tetravalent Vaccine or a Placebo |
| End point description:<br>Geometric mean titers against each of the 4 serotypes of dengue virus strains were assessed using the plaque reduction neutralization test (PRNT) in a pre-defined subset of subjects. Antibody titers against each dengue virus serotype strain were assessed in Full Analysis Set for Immunogenicity (FASI), which included a subset of subjects who received at least one dose of vaccine and had a blood sample drawn and result available after the dose. Here, 'n' = subjects with available data for each specified category. |                                                                                                                                                                                   |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 | Secondary                                                                                                                                                                         |
| End point timeframe:<br>Pre-injection 1, 28 days post Injections 2 and 3, 13 months (Visit 07) and 60 months (Visit 12) post-injection 3                                                                                                                                                                                                                                                                                                                                                                                                                       |                                                                                                                                                                                   |

| End point values                                   | CYD Dengue Vaccine Group | Placebo Group       |  |  |
|----------------------------------------------------|--------------------------|---------------------|--|--|
| Subject group type                                 | Reporting group          | Reporting group     |  |  |
| Number of subjects analysed                        | 1323                     | 660                 |  |  |
| Units: Titers 1/Dilution (1/dil)                   |                          |                     |  |  |
| geometric mean (confidence interval 95%)           |                          |                     |  |  |
| Dengue virus Serotype 1; Pre-Inj. 1(n=1309,655)    | 38.3 (33.8 to 43.5)      | 42.1 (35 to 50.6)   |  |  |
| Dengue virus Serotype 1; Post Inj. 2 (n=1317,654)  | 153 (137 to 170)         | 46.1 (38.2 to 55.7) |  |  |
| Dengue virus Serotype 1; Post Inj. 3 (n=1316,657)  | 166 (150 to 183)         | 46.6 (38.7 to 56.1) |  |  |
| Serotype 1;Year 1 Post Inj.3(V 07) (n=1290,634)    | 105 (92.8 to 119)        | 57.2 (46.9 to 69.8) |  |  |
| Serotype 1; Year 5 Post Inj. 3 (V 12) (n=1275,640) | 81.2 (72.5 to 91.0)      | 77.6 (65.4 to 92.2) |  |  |
| Dengue virus Serotype 2; Pre-Inj. 1 (n=1313,654)   | 55.3 (48.7 to 62.9)      | 62.1 (51.7 to 74.7) |  |  |
| Dengue virus Serotype 2; Post Inj. 2 (n=1316,655)  | 360 (329 to 394)         | 69.5 (57.7 to 83.6) |  |  |
| Dengue virus Serotype 2; Post Inj. 3 (n=1314, 657) | 355 (327 to 386)         | 68.5 (57.1 to 82.2) |  |  |
| Serotype 2; Year 1 Post-Inj. 3 (V 07) (n=1298,640) | 194 (175 to 214)         | 78.1 (64.8 to 94.0) |  |  |
| Serotype 2; Year 5 Post-Inj. 3 (V 12) (n=1275,640) | 144 (130 to 160)         | 102 (86.8 to 120)   |  |  |
| Dengue virus Serotype 3; Pre-Inj. 1 (n=1307,650)   | 40.1 (35.6 to 45.1)      | 40.7 (34.5 to 48)   |  |  |
| Dengue virus Serotype 3; Post Inj. 2 (n=1313,656)  | 203 (184 to 223)         | 40.8 (34.6 to 48.1) |  |  |
| Dengue virus Serotype 3; Post Inj. 3 (n=1314,657)  | 207 (189 to 226)         | 42.5 (36.2 to 49.9) |  |  |
| Serotype 3; Year 1 Post Inj. 3 (V 07) (n=1298,639) | 186 (168 to 206)         | 62.1 (51.8 to 74.6) |  |  |
| Serotype 3; Year 5 Post Inj. 3 (V 12) (n=1275,640) | 120 (108 to 133)         | 76.2 (65.3 to 89.0) |  |  |
| Dengue virus Serotype 4; Pre Inj. 1 (n=1313,653)   | 25.3 (22.9 to 28)        | 26.2 (22.6 to 30.3) |  |  |
| Dengue virus Serotype 4; Post Inj. 2 (n=1318,655)  | 151 (139 to 163)         | 24.4 (21.3 to 28.1) |  |  |
| Dengue virus Serotype 4; Post Inj. 3 (n=1315,657)  | 151 (141 to 162)         | 26 (22.6 to 29.8)   |  |  |
| Serotype 4; Year 1 Post Inj. 3 (V 07) (n=1293,621) | 85.5 (78.5 to 93)        | 26.0 (22.4 to 30.3) |  |  |
| Serotype 4; Year 5 Post Inj. 3 (V 12) (n=1275,640) | 65.7 (60.3 to 71.6)      | 40.1 (34.8 to 46.1) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Subjects With Antibody Titers $\geq 10$ 1/Dil Against Each Dengue Virus Serotype Strain Before and Following Inj. With CYD Dengue Vaccine or Placebo

|                 |                                                                                                                  |
|-----------------|------------------------------------------------------------------------------------------------------------------|
| End point title | Percentage of Subjects With Antibody Titers $\geq 10$ 1/Dil Against Each Dengue Virus Serotype Strain Before and |
|-----------------|------------------------------------------------------------------------------------------------------------------|

## End point description:

Percentage of subjects with antibody titers  $\geq 10$  (1/dil) against each serotypes of the dengue virus strains were assessed using PRNT in a pre-defined subset of subjects. Antibody titers against each dengue virus serotype strain were assessed in FASI. Here, 'n' = subjects with available data for each specified category.

## End point type

Secondary

## End point timeframe:

Pre-injection 1, 28 days post Injections 2 and 3, 13 months (V 07) and 60 months (V 12) post-injection 3

| End point values                                      | CYD Dengue Vaccine Group | Placebo Group   |  |  |
|-------------------------------------------------------|--------------------------|-----------------|--|--|
| Subject group type                                    | Reporting group          | Reporting group |  |  |
| Number of subjects analysed                           | 1323                     | 660             |  |  |
| Units: Percentage of subjects                         |                          |                 |  |  |
| number (not applicable)                               |                          |                 |  |  |
| Dengue virus Serotype 1; Pre-Inj. 1<br>(n=1309,655)   | 52.0                     | 51.3            |  |  |
| Dengue virus Serotype 1; Post Inj. 2<br>(n=1317,654)  | 88.9                     | 54.4            |  |  |
| Dengue virus Serotype 1; Post-Inj. 3<br>(n=1316,657)  | 94.0                     | 55.4            |  |  |
| Serotype 1; Year 1 Post-Inj. 3 (V 07)<br>(n=1290,634) | 79.8                     | 55.7            |  |  |
| Serotype 1; Year 5 Post-Inj 3 (V 12)<br>(n=1275,640)  | 76.2                     | 70.0            |  |  |
| Dengue virus Serotype 2; Pre-Inj. 1<br>(n=1313,654)   | 58.0                     | 59.3            |  |  |
| Dengue virus Serotype 2; Post-Inj. 2<br>(n=1316,655)  | 97.3                     | 62.4            |  |  |
| Dengue virus Serotype 2; Post-Inj. 3<br>(n=1314,657)  | 98.7                     | 61.8            |  |  |
| Serotype 2; Year 1 Post-Inj. 3 (V 07)<br>(n=1298,640) | 92.0                     | 65.8            |  |  |
| Serotype 2; Year 5 Post-inj 3 (V 12)<br>(n=1275,640)  | 86.0                     | 75.2            |  |  |
| Dengue virus Serotype 3; Pre-Inj. 1<br>(n=1307,650)   | 56.8                     | 59.4            |  |  |
| Dengue virus Serotype 3; Post-Inj. 2<br>(n=1313,656)  | 95.7                     | 60.2            |  |  |
| Dengue virus Serotype 3; Post-Inj. 3<br>(n=1314,657)  | 97.0                     | 61.0            |  |  |
| Serotype 3; Year 1 Post-Inj. 3 (V 07)<br>(n=1298,639) | 93.6                     | 62.6            |  |  |
| Serotype 3; Year5 Post-Inj. 3 (V 12)<br>(n=1275,640)  | 87.4                     | 75.6            |  |  |
| Dengue virus Serotype 4; Pre-Inj. 1<br>(n=1313,653)   | 51.6                     | 50.7            |  |  |
| Dengue virus Serotype 4; Post-Inj. 2<br>(n=1318,655)  | 95.1                     | 51.8            |  |  |
| Dengue virus Serotype 4; Post-Inj. 3<br>(n=1315,657)  | 97.0                     | 53.9            |  |  |
| Serotype 4; Year 1 Post-Inj 3 (V 07)<br>(n=1293,621)  | 89.4                     | 50.6            |  |  |
| Serotype 4; Year 5 Post-Inj 3 (V 12)<br>(n=1275,640)  | 83.8                     | 65.0            |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Subjects With Solicited Injection Site Reactions Following Any and Each Inj. With Either CYD Dengue Vaccine or a Placebo

|                 |                                                                                                                                    |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Subjects With Solicited Injection Site Reactions Following Any and Each Inj. With Either CYD Dengue Vaccine or a Placebo |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Solicited injection site reactions: Pain, Erythema, and Swelling. Grade 3 reactions (2-11 years) - Pain: incapacitating, unable to perform usual activities; Erythema and Swelling,  $\geq 50$  mm. Grade 3 Solicited injection site reactions (12-14 years): Pain, Significant, prevents daily activity; Erythema and Swelling,  $>100$  mm. Solicited injection site reactions were assessed in a subset of the Safety Analysis Set, which included all subjects who received at least one dose of study vaccine. Here, 'n' = subjects with available data for each specified category.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Within 7 days after injection

| End point values                                   | CYD Dengue Vaccine Group | Placebo Group   |  |  |
|----------------------------------------------------|--------------------------|-----------------|--|--|
| Subject group type                                 | Reporting group          | Reporting group |  |  |
| Number of subjects analysed                        | 1334                     | 663             |  |  |
| Units: Number of subjects                          |                          |                 |  |  |
| number (not applicable)                            |                          |                 |  |  |
| Inj. site Pain (Post any Inj.)<br>(n=1332,663)     | 614                      | 275             |  |  |
| Inj. site Erythema (Post-any Inj.)<br>(n=1332,663) | 107                      | 52              |  |  |
| Inj. site Swelling (Post any Inj.)<br>(n=1332,663) | 68                       | 33              |  |  |
| Inj. site Pain (Post-Inj. 1) (n=1332,663)          | 406                      | 196             |  |  |
| Grade 3 Inj. site Pain (Post- Inj. 1)(n=1332,663)  | 1                        | 0               |  |  |
| Inj. site Erythema (Post Inj. 1)<br>(n=1332,663)   | 63                       | 35              |  |  |
| Grade 3 Inj. site Erythema(Post Inj.1)(n=1332,663) | 0                        | 0               |  |  |
| Inj. site Swelling (Post Inj.1)(n=1332,663)        | 40                       | 19              |  |  |
| Grade 3 Inj. site Swelling(Post Inj.1)(n=1332,663) | 0                        | 0               |  |  |
| Inj. site Pain (Post Inj.2)(n=1319,658)            | 303                      | 135             |  |  |
| Grade 3 Inj. site Pain (Post- Inj.2)(n=1319,658)   | 0                        | 0               |  |  |
| Inj. site Erythema (Post Inj.2)(n=1319,658)        | 43                       | 20              |  |  |

|                                                    |     |     |  |  |
|----------------------------------------------------|-----|-----|--|--|
| Grade 3 Inj. site Erythema(Post Inj.2)(n=1319,658) | 0   | 0   |  |  |
| Inj. site Swelling (Post Inj.2)(n=1319,658)        | 25  | 7   |  |  |
| Grade 3 Inj. site Swelling(Post Inj.2)(n=1319,658) | 0   | 0   |  |  |
| Inj. site Pain (Post Inj. 3)(n=1313,654)           | 283 | 118 |  |  |
| Grade 3 Inj. site Pain (Post Inj. 3)(n=1313,654)   | 0   | 0   |  |  |
| Inj. site Erythema (Post Inj.3)(n=1313,654)        | 36  | 16  |  |  |
| Grade 3 Inj. site Erythema(Post Inj.3)(n=1313,654) | 0   | 1   |  |  |
| Inj. site Swelling (Post Inj.3)(n=1313,654)        | 19  | 10  |  |  |
| Grade 3 Inj. site Swelling(Post Inj.3)(n=1313,654) | 0   | 0   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Symptomatic VCD Cases Due to Any Serotype Occurring 28 Days Post-Dose 1 Following Inj. With Either CYD Dengue Vaccine or a Placebo

|                 |                                                                                                                                              |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Symptomatic VCD Cases Due to Any Serotype Occurring 28 Days Post-Dose 1 Following Inj. With Either CYD Dengue Vaccine or a Placebo |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Symptomatic VCD cases were defined as occurrence of acute febrile illness (temperature  $\geq 38^{\circ}\text{C}$  on at least 2 consecutive days) and confirmation of dengue virus infection by dengue RT-PCR and/or dengue NS1 ELISA. Vaccine efficacy was defined as 1 minus the ratio of density incidence due to any serotype after at least 1 dose in the CYD Dengue Vaccine Group over the density incidence of the Placebo Vaccine Group. Number of symptomatic VCD cases were assessed in the Full Analysis Set for Efficacy, which included subjects who received at least 1 dose of study vaccine.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

28 days post-injection 1 and up to 13 months post-injection 3

| End point values            | CYD Dengue Vaccine Group | Placebo Group   |  |  |
|-----------------------------|--------------------------|-----------------|--|--|
| Subject group type          | Reporting group          | Reporting group |  |  |
| Number of subjects analysed | 6848                     | 3424            |  |  |
| Units: Cases                |                          |                 |  |  |
| number (not applicable)     | 276                      | 302             |  |  |

## Statistical analyses

|                            |                                         |
|----------------------------|-----------------------------------------|
| Statistical analysis title | CYD Dengue Vaccine Group, Placebo Group |
|----------------------------|-----------------------------------------|

**Statistical analysis description:**

The statistical methodology was based on the use of the two-sided 95% CI of the vaccine efficacy (expressed in %) calculated using the exact method conditional on the total number of cases in both groups.

|                                         |                                          |
|-----------------------------------------|------------------------------------------|
| Comparison groups                       | CYD Dengue Vaccine Group v Placebo Group |
| Number of subjects included in analysis | 10272                                    |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | other                                    |
| Parameter estimate                      | Vaccine Efficacy                         |
| Point estimate                          | 55.4                                     |
| Confidence interval                     |                                          |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | 47.3                                     |
| upper limit                             | 62.3                                     |

**Secondary: Number of Symptomatic VCD Cases Meeting 1997 World Health Organization (WHO) Criteria During the Surveillance Expansion Period Due to Any Serotype Following Inj. With Either CYD Dengue Vaccine or a Placebo**

|                 |                                                                                                                                                                                                               |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Symptomatic VCD Cases Meeting 1997 World Health Organization (WHO) Criteria During the Surveillance Expansion Period Due to Any Serotype Following Inj. With Either CYD Dengue Vaccine or a Placebo |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

**End point description:**

The 1997 WHO criteria are: a) Fever: acute onset, high ( $\geq 38^{\circ}\text{C}$ ) and continuous, for 2 to 7 days and (b) any of the following: thrombocytopenia (platelet  $\leq 100 \times 10^9/\text{L}$ ) and plasma leakage as shown by hematocrit increased by 20% or more or pleural effusion and/or ascites and/or hypoalbuminemia. The first two clinical criteria plus thrombocytopenia and signs of plasma leakage are enough to establish diagnosis of Dengue hemorrhagic fever (DHF). DHF was graded as follows: Grade I: Fever accompanied by non-specific constitutional symptoms; the only hemorrhagic manifestation is a positive tourniquet test; Grade II: Spontaneous bleeding in addition to the manifestations of Grade I subjects, usually in the form of skin and/or other hemorrhages; Grade III: Circulatory failure manifested by rapid and weak pulse, narrowing of pulse pressure (20mmHg or less) or hypotension, with the presence of cold clammy skin and restlessness; and Grade IV: Profound shock with undetectable blood pressure and pulse.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

**End point timeframe:**

From consent to participate in Surveillance Expansion Period to 60 months post-injection 3 (up to Month 72)

| <b>End point values</b>                  | CYD Dengue Vaccine Group | Placebo Group   |  |  |
|------------------------------------------|--------------------------|-----------------|--|--|
| Subject group type                       | Reporting group          | Reporting group |  |  |
| Number of subjects analysed              | 6327                     | 3138            |  |  |
| Units: Cases                             |                          |                 |  |  |
| number (not applicable)                  |                          |                 |  |  |
| Due to Any of the 4 Serotypes: Any Grade | 19                       | 12              |  |  |
| Due to Any of the 4 Serotypes: Grade I   | 5                        | 3               |  |  |
| Due to Any of the 4 Serotypes: Grade II  | 11                       | 8               |  |  |
| Due to Any of the 4 Serotypes: Grade III | 3                        | 1               |  |  |

|                                         |   |   |  |  |
|-----------------------------------------|---|---|--|--|
| Due to Any of the 4 Serotypes: Grade IV | 0 | 0 |  |  |
|-----------------------------------------|---|---|--|--|

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Clinically Severe VCD Cases During the Surveillance Expansion Period Due to Any Serotype Following Inj. With Either CYD Dengue Vaccine or a Placebo

|                 |                                                                                                                                                               |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Clinically Severe VCD Cases During the Surveillance Expansion Period Due to Any Serotype Following Inj. With Either CYD Dengue Vaccine or a Placebo |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The severity of VCD cases was assessed by an IDMC based on a medical review of cases and any of the following criteria: 1) Platelet count  $\leq 100000/\mu\text{L}$  and bleeding (tourniquet, petechiae or any bleeding) plus plasma leakage 2) Shock (pulse pressure  $\leq 20\text{ mmHg}$  in a child, or hypotension [ $\leq 90\text{ mmHg}$ ] with tachycardia, weak pulse and poor perfusion) 3) Bleeding requiring blood transfusion 4) Encephalopathy i.e. Unconsciousness or poor conscious state or fitting not attributable to simple febrile convulsion or focal neurological signs. Poor conscious state or unconsciousness must be supported by Glasgow Coma Scale (GCS) score. 5) Liver impairment (AST  $1000\text{ IU/L}$  or prothrombin time [PT] International normalized ratio [INR]  $> 1.5$ ) excluding other causes of viral hepatitis 6) Impaired kidney function (serum creatinine  $\geq 1.5\text{ mg/dL}$ ) 7) Myocarditis, pericarditis or clinical heart failure supported by Chest X-Ray (CXR), echocardiography, electrocardiogram (ECG) or cardiac enzymes. Full Analysis Set for SEP.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From consent to participate in the Surveillance Expansion Period to 60 months post-injection 3 (up to Month 72)

| End point values            | CYD Dengue Vaccine Group | Placebo Group   |  |  |
|-----------------------------|--------------------------|-----------------|--|--|
| Subject group type          | Reporting group          | Reporting group |  |  |
| Number of subjects analysed | 6327                     | 3138            |  |  |
| Units: Cases                |                          |                 |  |  |
| number (not applicable)     | 21                       | 12              |  |  |

## Statistical analyses

No statistical analyses for this end point

### Secondary: Number of Symptomatic VCD Cases Due to Any Serotype 28 Days Post-Dose 2 Following Inj. With Either CYD Dengue Vaccine or a Placebo

|                 |                                                                                                                                    |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Symptomatic VCD Cases Due to Any Serotype 28 Days Post-Dose 2 Following Inj. With Either CYD Dengue Vaccine or a Placebo |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Symptomatic VCD cases were defined as occurrence of acute febrile illness (temperature  $\geq 38^\circ\text{C}$  on at least 2 consecutive days) and confirmation of dengue virus infection by dengue RT-PCR and/or dengue

NS1 ELISA. Vaccine efficacy was defined as 1 minus the ratio of density incidence due to any serotype after at least 1 dose in the CYD Dengue Vaccine Group over the density incidence of the Placebo Vaccine Group. Number of symptomatic VCD cases were assessed in the Other Efficacy Analysis Set, which included subjects who received at least 2 doses of study vaccine.

|                                                               |           |
|---------------------------------------------------------------|-----------|
| End point type                                                | Secondary |
| End point timeframe:                                          |           |
| 28 days post-injection 2 and up to 13 months post-injection 3 |           |

| End point values            | CYD Dengue Vaccine Group | Placebo Group   |  |  |
|-----------------------------|--------------------------|-----------------|--|--|
| Subject group type          | Reporting group          | Reporting group |  |  |
| Number of subjects analysed | 6793                     | 3397            |  |  |
| Units: Cases                |                          |                 |  |  |
| number (not applicable)     | 205                      | 238             |  |  |

## Statistical analyses

|                                   |                                         |
|-----------------------------------|-----------------------------------------|
| <b>Statistical analysis title</b> | CYD Dengue Vaccine Group, Placebo Group |
|-----------------------------------|-----------------------------------------|

Statistical analysis description:

The statistical methodology was based on the use of the two-sided 95% CI of the vaccine efficacy (expressed in %) calculated using the exact method conditional on the total number of cases in both groups.

|                                         |                                          |
|-----------------------------------------|------------------------------------------|
| Comparison groups                       | CYD Dengue Vaccine Group v Placebo Group |
| Number of subjects included in analysis | 10190                                    |
| Analysis specification                  | Pre-specified                            |
| Analysis type                           | other                                    |
| Parameter estimate                      | Vaccine Efficacy                         |
| Point estimate                          | 57.9                                     |
| Confidence interval                     |                                          |
| level                                   | 95 %                                     |
| sides                                   | 2-sided                                  |
| lower limit                             | 49                                       |
| upper limit                             | 65.2                                     |

## Secondary: Number of Symptomatic VCD Cases Due to Any Serotype During the Active Phase in Either CYD Dengue Vaccine or Placebo Group

|                 |                                                                                                                           |
|-----------------|---------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Symptomatic VCD Cases Due to Any Serotype During the Active Phase in Either CYD Dengue Vaccine or Placebo Group |
|-----------------|---------------------------------------------------------------------------------------------------------------------------|

End point description:

Symptomatic VCD cases were defined as occurrence of acute febrile illness (temperature  $\geq 38^{\circ}\text{C}$  on at least 2 consecutive days) and confirmation of dengue virus infection by dengue RT-PCR and/or dengue NS1 ELISA. Vaccine efficacy was defined as 1 minus the ratio of density incidence due to any serotype after at least 1 dose in the CYD Dengue Vaccine Group over the density incidence of the Placebo Vaccine Group. Number of symptomatic VCD cases were assessed in the Full Analysis Set for Efficacy, which included all subjects who received at least 1 injection.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|



End point timeframe:

Day 0 up to 13 months post-injection 3

| End point values            | CYD Dengue Vaccine Group | Placebo Group   |  |  |
|-----------------------------|--------------------------|-----------------|--|--|
| Subject group type          | Reporting group          | Reporting group |  |  |
| Number of subjects analysed | 6848                     | 3424            |  |  |
| Units: Cases                |                          |                 |  |  |
| number (not applicable)     | 286                      | 309             |  |  |

## Statistical analyses

| Statistical analysis title                                                                                                                                                                                                                        | CYD Dengue Vaccine Group, Placebo Group  |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------|
| Statistical analysis description:<br>The statistical methodology was based on the use of the two-sided 95% CI of the vaccine efficacy (expressed in %) calculated using the exact method conditional on the total number of cases in both groups. |                                          |
| Comparison groups                                                                                                                                                                                                                                 | CYD Dengue Vaccine Group v Placebo Group |
| Number of subjects included in analysis                                                                                                                                                                                                           | 10272                                    |
| Analysis specification                                                                                                                                                                                                                            | Pre-specified                            |
| Analysis type                                                                                                                                                                                                                                     | other                                    |
| Parameter estimate                                                                                                                                                                                                                                | Vaccine Efficacy                         |
| Point estimate                                                                                                                                                                                                                                    | 54.8                                     |
| Confidence interval                                                                                                                                                                                                                               |                                          |
| level                                                                                                                                                                                                                                             | 95 %                                     |
| sides                                                                                                                                                                                                                                             | 2-sided                                  |
| lower limit                                                                                                                                                                                                                                       | 46.8                                     |
| upper limit                                                                                                                                                                                                                                       | 61.7                                     |

## Secondary: Number of Clinically Severe VCD Cases Throughout the Trial Due to Any Serotype Following Inj. With Either CYD Dengue Vaccine or a Placebo

|                 |                                                                                                                                           |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Clinically Severe VCD Cases Throughout the Trial Due to Any Serotype Following Inj. With Either CYD Dengue Vaccine or a Placebo |
|-----------------|-------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

The severity of VCD cases was assessed by an IDMC based on a medical review of cases and any of the following criteria: 1) Platelet count  $\leq 100000\mu\text{l}$  and bleeding (tourniquet, petechiae or any bleeding) plus plasma leakage 2) Shock (pulse pressure  $\leq 20\text{mmHg}$  in a child, or hypotension [ $\leq 90\text{ mmHg}$ ] with tachycardia, weak pulse and poor perfusion) 3) Bleeding requiring blood transfusion 4) Encephalopathy i.e. Unconsciousness or poor conscious state or fitting not attributable to simple febrile convulsion or focal neurological signs. Poor conscious state or unconsciousness must be supported by GCS score. 5) Liver impairment (AST  $>1000\text{IU/L}$  or PT International normalized ratio [INR]  $>1.5$ ) excluding other causes of viral hepatitis 6) Impaired kidney function (serum creatinine  $\geq 1.5\text{mg/dL}$ ) 7) Myocarditis, pericarditis or clinical heart failure supported by CXR, echocardiography, ECG or cardiac enzymes. Number of clinically severe VCD cases were assessed in the Safety Analysis Set.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 0 to the end of study (up to 72 months)

| End point values            | CYD Dengue Vaccine Group | Placebo Group   |  |  |
|-----------------------------|--------------------------|-----------------|--|--|
| Subject group type          | Reporting group          | Reporting group |  |  |
| Number of subjects analysed | 6745                     | 3369            |  |  |
| Units: Cases                |                          |                 |  |  |
| number (not applicable)     | 61                       | 41              |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects With Systemic Reactions Following Any and Each Inj. With Either CYD Dengue Vaccine or a Placebo

|                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |                                                                                                                    |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------|
| End point title                                                                                                                                                                                                                                                                                                                                                                                                                                                          | Number of Subjects With Systemic Reactions Following Any and Each Inj. With Either CYD Dengue Vaccine or a Placebo |
| End point description:                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                    |
| Solicited systemic reactions: Fever (Temperature), Headache, Malaise, Myalgia, and Asthenia. Grade 3 reactions- Fever: $\geq 39^{\circ}\text{C}$ ; Headache, Malaise, Myalgia, and Asthenia, Significant, prevents daily activity. Solicited systemic reactions were assessed in a subset of the Safety Analysis Set, which included all subjects who received at least one dose of study vaccine. Here, 'n' = subjects with available data for each specified category. |                                                                                                                    |
| End point type                                                                                                                                                                                                                                                                                                                                                                                                                                                           | Secondary                                                                                                          |
| End point timeframe:                                                                                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                    |
| Within 14 days after injection                                                                                                                                                                                                                                                                                                                                                                                                                                           |                                                                                                                    |

| End point values                                 | CYD Dengue Vaccine Group | Placebo Group   |  |  |
|--------------------------------------------------|--------------------------|-----------------|--|--|
| Subject group type                               | Reporting group          | Reporting group |  |  |
| Number of subjects analysed                      | 1334                     | 663             |  |  |
| Units: Number of subjects                        |                          |                 |  |  |
| number (not applicable)                          |                          |                 |  |  |
| Fever (Post any injection) (n=1332,663)          | 248                      | 118             |  |  |
| Headache (Post any injection) (n=1332,663)       | 562                      | 259             |  |  |
| Malaise (Post any injection) (n=1332,663)        | 476                      | 239             |  |  |
| Myalgia (Post any injection) (n=1332,663)        | 414                      | 197             |  |  |
| Asthenia (Post any injection) (n=1332,663)       | 378                      | 167             |  |  |
| Fever (Post-injection 1) (n=1330,663)            | 103                      | 45              |  |  |
| Grade 3 Fever (Post-injection 1) (n=1330,663)    | 18                       | 7               |  |  |
| Headache (Post-injection 1) (n=1332,663)         | 387                      | 168             |  |  |
| Grade 3 Headache (Post-injection 1) (n=1332,663) | 7                        | 6               |  |  |

|                                                     |     |     |  |  |
|-----------------------------------------------------|-----|-----|--|--|
| Malaise (Post-injection 1) (n=1332,663)             | 312 | 148 |  |  |
| Grade 3 Malaise (Post-injection 1)<br>(n=1332,663)  | 7   | 4   |  |  |
| Myalgia (Post-injection 1) (n=1332,663)             | 255 | 124 |  |  |
| Grade 3 Myalgia (Post-injection 1)<br>(n=1332,663)  | 2   | 2   |  |  |
| Asthenia (Post-injection 1)<br>(n=1332,663)         | 229 | 97  |  |  |
| Grade 3 Asthenia (Post-injection 1)<br>(n=1332,663) | 5   | 5   |  |  |
| Fever (Post-injection 2) (n=1320,657)               | 90  | 44  |  |  |
| Grade 3 Fever (Post-injection 2)<br>(n=1320,657)    | 19  | 9   |  |  |
| Headache (Post-injection 2)<br>(n=1319,658)         | 247 | 118 |  |  |
| Grade 3 Headache (Post-injection 2)<br>(n=1319,658) | 12  | 3   |  |  |
| Malaise (Post-injection 2) (n=1319,658)             | 192 | 100 |  |  |
| Grade 3 Malaise (Post-injection 2)<br>(n=1319,658)  | 6   | 4   |  |  |
| Myalgia (Post-injection 2) (n=1319,658)             | 174 | 92  |  |  |
| Grade 3 Myalgia (Post-injection 2)<br>(n=1319,658)  | 3   | 0   |  |  |
| Asthenia (Post-injection 2)<br>(n=1319,658)         | 158 | 74  |  |  |
| Grade 3 Asthenia (Post-injection 2)<br>(n=1319,658) | 5   | 6   |  |  |
| Fever (Post-injection 3) (n=1309,654)               | 76  | 39  |  |  |
| Grade 3 Fever (Post-injection 3)<br>(n=1309,654)    | 16  | 2   |  |  |
| Headache (Post-injection 3)<br>(n=1313,654)         | 219 | 113 |  |  |
| Grade 3 Headache (Post-injection 3)<br>(n=1313,654) | 6   | 1   |  |  |
| Malaise (Post-injection 3) (n=1313,654)             | 183 | 104 |  |  |
| Grade 3 Malaise (Post-injection 3)<br>(n=1313,654)  | 7   | 1   |  |  |
| Myalgia (Post-injection 3) (n=1313,654)             | 156 | 76  |  |  |
| Grade 3 Myalgia (Post-injection 3)<br>(n=1313,654)  | 3   | 0   |  |  |
| Asthenia (Post-injection 3)<br>(n=1313,654)         | 142 | 73  |  |  |
| Grade 3 Asthenia (Post-injection 3)<br>(n=1313,654) | 4   | 2   |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Hospitalized VCD Cases During the Surveillance Expansion Period Due to Any Serotype Following Inj. With Either CYD Dengue Vaccine or a Placebo

|                 |                                                                                                                                                          |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Hospitalized VCD Cases During the Surveillance Expansion Period Due to Any Serotype Following Inj. With Either CYD Dengue Vaccine or a Placebo |
|-----------------|----------------------------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Hospitalized VCD cases were defined as VCD confirmed by dengue RT –PCR and/or dengue NS1 ELISA in subjects with acute febrile illness (temperature  $\geq 38^{\circ}\text{C}$  on at least 2 consecutive days) requiring hospitalization.

Number of hospitalized VCD cases were assessed in the Safety Analysis Set.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From consent to participate in the Surveillance Expansion Period to 60 months post-injection 3 (up to Month 72)

| End point values            | CYD Dengue Vaccine Group | Placebo Group   |  |  |
|-----------------------------|--------------------------|-----------------|--|--|
| Subject group type          | Reporting group          | Reporting group |  |  |
| Number of subjects analysed | 6848                     | 3424            |  |  |
| Units: Cases                |                          |                 |  |  |
| number (not applicable)     | 74                       | 48              |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Hospitalized VCD Cases Throughout the Trial Due to Any Serotype Following Inj. With Either CYD Dengue Vaccine or a Placebo

|                 |                                                                                                                                      |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Hospitalized VCD Cases Throughout the Trial Due to Any Serotype Following Inj. With Either CYD Dengue Vaccine or a Placebo |
|-----------------|--------------------------------------------------------------------------------------------------------------------------------------|

End point description:

Hospitalized VCD cases were defined as VCD confirmed by dengue RT –PCR and/or dengue NS1 ELISA in subjects with acute febrile illness (temperature  $\geq 38^{\circ}\text{C}$  on at least 2 consecutive days) requiring hospitalization.

Number of VCD cases were assessed in the Safety Analysis Set.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 0 to the end of study (up to 72 months)

| End point values            | CYD Dengue Vaccine Group | Placebo Group   |  |  |
|-----------------------------|--------------------------|-----------------|--|--|
| Subject group type          | Reporting group          | Reporting group |  |  |
| Number of subjects analysed | 6745                     | 3369            |  |  |
| Units: Cases                |                          |                 |  |  |
| number (not applicable)     | 210                      | 154             |  |  |

## Statistical analyses

## Secondary: Number of Symptomatic VCD Cases Meeting 1997 WHO Criteria Throughout the Trial Due to Any Serotype Following Inj. With Either CYD Dengue Vaccine or a Placebo

|                 |                                                                                                                                                               |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|
| End point title | Number of Symptomatic VCD Cases Meeting 1997 WHO Criteria Throughout the Trial Due to Any Serotype Following Inj. With Either CYD Dengue Vaccine or a Placebo |
|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------|

### End point description:

The 1997 WHO criteria are: a) Fever: acute onset, high ( $\geq 38^{\circ}\text{C}$ ) and continuous, for 2 to 7 days and (b) any of the following: thrombocytopenia (platelet  $\leq 100 \times 10^9/\text{L}$ ) and plasma leakage as shown by hematocrit increased by 20% or more or pleural effusion and/or ascites and/or hypoalbuminemia. The first two clinical criteria plus thrombocytopenia and signs of plasma leakage are enough to establish diagnosis of DHF. DHF was graded as follows: Grade I: Fever accompanied by non-specific constitutional symptoms; the only hemorrhagic manifestation is a positive tourniquet test; Grade II: Spontaneous bleeding in addition to the manifestations of Grade I subjects, usually in the form of skin and/or other hemorrhages; Grade III: Circulatory failure manifested by rapid and weak pulse, narrowing of pulse pressure (20 mmHg or less) or hypotension, with the presence of cold clammy skin and restlessness; and Grade IV: Profound shock with undetectable blood pressure and pulse. Full Analysis Set for SEP.

|                |           |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

### End point timeframe:

Day 0 to the end of study (up to 72 months)

| End point values                         | CYD Dengue Vaccine Group | Placebo Group   |  |  |
|------------------------------------------|--------------------------|-----------------|--|--|
| Subject group type                       | Reporting group          | Reporting group |  |  |
| Number of subjects analysed              | 6745                     | 3369            |  |  |
| Units: Cases                             |                          |                 |  |  |
| number (not applicable)                  |                          |                 |  |  |
| Due to Any of the 4 Serotypes: Any Grade | 55                       | 41              |  |  |
| Due to Any of the 4 Serotypes: Grade I   | 14                       | 9               |  |  |
| Due to Any of the 4 Serotypes: Grade II  | 37                       | 29              |  |  |
| Due to Any of the 4 Serotypes: Grade III | 4                        | 3               |  |  |
| Due to Any of the 4 Serotypes: Grade IV  | 0                        | 0               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

AE data were collected from Day 0 (post-vaccination) up to 60 months post-injection 3 (up to 72 months).

Adverse event reporting additional description:

All vaccinated subjects were assessed for serious AEs during the trial. Non-serious AEs were assessed in a subset of subjects from each group, and included solicited injection site and systemic reactions (within 7 and 14 days after injection), as well as unsolicited non-serious AEs (28 days after injection).

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 14.0 |
|--------------------|------|

### Reporting groups

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | CYD Dengue Vaccine Group |
|-----------------------|--------------------------|

Reporting group description:

Subjects received 3 doses of CYD dengue vaccine; one each at 0, 6, and 12 months and were followed up to 60 months after last vaccination (for a total duration of up to 72 months).

|                       |               |
|-----------------------|---------------|
| Reporting group title | Placebo Group |
|-----------------------|---------------|

Reporting group description:

Subjects received 3 doses of placebo matched to vaccine; one each at 0, 6, and 12 months and were followed up to 60 months after last vaccination (for a total duration of up to 72 months).

| Serious adverse events                                              | CYD Dengue Vaccine Group | Placebo Group          |  |
|---------------------------------------------------------------------|--------------------------|------------------------|--|
| Total subjects affected by serious adverse events                   |                          |                        |  |
| subjects affected / exposed                                         | 947 / 6848<br>(13.83%)   | 552 / 3424<br>(16.12%) |  |
| number of deaths (all causes)                                       | 10                       | 4                      |  |
| number of deaths resulting from adverse events                      |                          |                        |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                          |                        |  |
| Acute Lymphocytic Leukaemia                                         |                          |                        |  |
| subjects affected / exposed                                         | 1 / 6848 (0.01%)         | 1 / 3424 (0.03%)       |  |
| occurrences causally related to treatment / all                     | 0 / 1                    | 0 / 1                  |  |
| deaths causally related to treatment / all                          | 0 / 0                    | 0 / 1                  |  |
| Angiofibroma                                                        |                          |                        |  |
| subjects affected / exposed                                         | 1 / 6848 (0.01%)         | 0 / 3424 (0.00%)       |  |
| occurrences causally related to treatment / all                     | 0 / 1                    | 0 / 0                  |  |
| deaths causally related to treatment / all                          | 0 / 0                    | 0 / 0                  |  |
| Benign Neoplasm Of Skin                                             |                          |                        |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Benign Soft Tissue Neoplasm                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bone Giant Cell Tumour Benign                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bone Sarcoma                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Breast Neoplasm                                 |                  |                  |  |
| subjects affected / exposed                     | 3 / 6848 (0.04%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ear Neoplasm                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fibroadenoma Of Breast                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fibrous Histiocytoma                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemangioma                                     |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 6848 (0.03%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lip Neoplasm Benign                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lipoma                                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 2 / 3424 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lymphangioma                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skin Papilloma                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 2 / 3424 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Soft Tissue Neoplasm                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Teratoma                                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vascular disorders                              |                  |                  |  |
| Aneurysm Ruptured                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Haematoma                                       |                  |                  |  |



|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypertension                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Surgical and medical procedures                 |                  |                  |  |
| Abortion Induced                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pregnancy, puerperium and perinatal conditions  |                  |                  |  |
| Abortion Complete                               |                  |                  |  |
| subjects affected / exposed                     | 3 / 6848 (0.04%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abortion Incomplete                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abortion Spontaneous                            |                  |                  |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abortion Spontaneous Incomplete                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abortion Threatened                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| Breech Presentation                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cephalo-Pelvic Disproportion                    |                  |                  |  |
| subjects affected / exposed                     | 3 / 6848 (0.04%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Eclampsia                                       |                  |                  |  |
| subjects affected / exposed                     | 3 / 6848 (0.04%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Ectopic Pregnancy                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| False Labour                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Foetal Distress Syndrome                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oligohydramnios                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Postpartum Haemorrhage                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 2 / 3424 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Premature Labour                                |                  |                  |  |

|                                                      |                  |                  |  |
|------------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                          | 4 / 6848 (0.06%) | 2 / 3424 (0.06%) |  |
| occurrences causally related to treatment / all      | 0 / 4            | 0 / 2            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Puerperal Pyrexia                                    |                  |                  |  |
| subjects affected / exposed                          | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Stillbirth                                           |                  |                  |  |
| subjects affected / exposed                          | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| General disorders and administration site conditions |                  |                  |  |
| Drowning                                             |                  |                  |  |
| subjects affected / exposed                          | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 1            | 0 / 0            |  |
| Hernia Obstructive                                   |                  |                  |  |
| subjects affected / exposed                          | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Pyrexia                                              |                  |                  |  |
| subjects affected / exposed                          | 2 / 6848 (0.03%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all      | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Immune system disorders                              |                  |                  |  |
| Allergy To Arthropod Bite                            |                  |                  |  |
| subjects affected / exposed                          | 1 / 6848 (0.01%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all      | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |
| Allergy To Arthropod Sting                           |                  |                  |  |
| subjects affected / exposed                          | 4 / 6848 (0.06%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all      | 0 / 4            | 0 / 1            |  |
| deaths causally related to treatment / all           | 0 / 0            | 0 / 0            |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| Anaphylactic Reaction                           |                  |                  |  |
| subjects affected / exposed                     | 3 / 6848 (0.04%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anaphylactic Shock                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 2 / 3424 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Drug Hypersensitivity                           |                  |                  |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Food Allergy                                    |                  |                  |  |
| subjects affected / exposed                     | 5 / 6848 (0.07%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypersensitivity                                |                  |                  |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%) | 2 / 3424 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Social circumstances                            |                  |                  |  |
| Child Abuse                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Physical Assault                                |                  |                  |  |
| subjects affected / exposed                     | 4 / 6848 (0.06%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Victim Of Child Abuse                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Victim Of Crime                                 |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Victim Of Sexual Abuse                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Reproductive system and breast disorders        |                  |                  |  |
| Acquired Phimosi                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Breast Mass                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dysfunctional Uterine Bleeding                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Endometriosis                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemorrhagic Ovarian Cyst                       |                  |                  |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ovarian Cyst                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ovarian Haemorrhage                             |                  |                  |  |

|                                                 |                   |                  |  |
|-------------------------------------------------|-------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Uterine Cervical Erosion                        |                   |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%)  | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Uterine Haemorrhage                             |                   |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Vaginal Haematoma                               |                   |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Respiratory, thoracic and mediastinal disorders |                   |                  |  |
| Adenoidal Hypertrophy                           |                   |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%)  | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Asphyxia                                        |                   |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Asthma                                          |                   |                  |  |
| subjects affected / exposed                     | 12 / 6848 (0.18%) | 9 / 3424 (0.26%) |  |
| occurrences causally related to treatment / all | 0 / 19            | 0 / 9            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Bronchial Hyperreactivity                       |                   |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Nasal Polyps                                    |                   |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nasal Septum Deviation                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neonatal Asphyxia                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pneumothorax                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Respiratory Acidosis                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sleep Apnoea Syndrome                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Upper Respiratory Tract Inflammation            |                  |                  |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Psychiatric disorders                           |                  |                  |  |
| Abnormal Behaviour                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Acute Psychosis                                 |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bipolar I Disorder                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bipolar Disorder                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mental Disorder                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Psychosomatic Disease                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Psychotic Disorder                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Schizophrenia                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Somatoform Disorder                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Suicide Attempt                                 |                  |                  |  |



|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 2 / 3424 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatobiliary disorders                         |                  |                  |  |
| Hepatitis                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Injury, poisoning and procedural complications  |                  |                  |  |
| Accident                                        |                  |                  |  |
| subjects affected / exposed                     | 4 / 6848 (0.06%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Adverse Event Following Immunisation            |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Animal Bite                                     |                  |                  |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%) | 4 / 3424 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Arthropod Bite                                  |                  |                  |  |
| subjects affected / exposed                     | 3 / 6848 (0.04%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Burns Second Degree                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chemical Poisoning                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| Chest Injury                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Clavicle Fracture                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Concussion                                      |                  |                  |  |
| subjects affected / exposed                     | 7 / 6848 (0.10%) | 2 / 3424 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Contusion                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ear Injury                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Electrical Burn                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Excoriation                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Eye Injury                                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Eyeball Rupture                                 |                  |                  |  |

|                                                 |                   |                  |  |
|-------------------------------------------------|-------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6848 (0.00%)  | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Facial Bones Fracture                           |                   |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Fall                                            |                   |                  |  |
| subjects affected / exposed                     | 15 / 6848 (0.22%) | 6 / 3424 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 16            | 0 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Femur Fracture                                  |                   |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Fibula Fracture                                 |                   |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%)  | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Foot Fracture                                   |                   |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Forearm Fracture                                |                   |                  |  |
| subjects affected / exposed                     | 9 / 6848 (0.13%)  | 4 / 3424 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 9             | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Foreign Body                                    |                   |                  |  |
| subjects affected / exposed                     | 5 / 6848 (0.07%)  | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 5             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Foreign Body In Eye                             |                   |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Genital Injury                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gun Shot Wound                                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hand Fracture                                   |                  |                  |  |
| subjects affected / exposed                     | 3 / 6848 (0.04%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Head Injury                                     |                  |                  |  |
| subjects affected / exposed                     | 5 / 6848 (0.07%) | 4 / 3424 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Humerus Fracture                                |                  |                  |  |
| subjects affected / exposed                     | 9 / 6848 (0.13%) | 2 / 3424 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Impacted Fracture                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Injury                                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 2 / 3424 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Intentional Overdose                            |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Joint Dislocation                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Joint Injury                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Laceration                                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ligament Sprain                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Limb Injury                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 3 / 3424 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lower Limb Fracture                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 2 / 3424 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Multiple Fractures                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Multiple Injuries                               |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Muscle Strain                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Near Drowning                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Open Wound                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Overdose                                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Poisoning Deliberate                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Postoperative Adhesion                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Postoperative Ileus                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Radius Fracture                                 |                  |                  |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 6 / 6848 (0.09%)  | 5 / 3424 (0.15%)  |  |
| occurrences causally related to treatment / all | 0 / 6             | 0 / 5             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Road Traffic Accident                           |                   |                   |  |
| subjects affected / exposed                     | 71 / 6848 (1.04%) | 38 / 3424 (1.11%) |  |
| occurrences causally related to treatment / all | 0 / 75            | 0 / 39            |  |
| deaths causally related to treatment / all      | 0 / 6             | 0 / 0             |  |
| Scrotal Haematoma                               |                   |                   |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 0 / 3424 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Snake Bite                                      |                   |                   |  |
| subjects affected / exposed                     | 4 / 6848 (0.06%)  | 0 / 3424 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Soft Tissue Injury                              |                   |                   |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 0 / 3424 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Sports Injury                                   |                   |                   |  |
| subjects affected / exposed                     | 5 / 6848 (0.07%)  | 1 / 3424 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 5             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Stab Wound                                      |                   |                   |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 0 / 3424 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Tendon Rupture                                  |                   |                   |  |
| subjects affected / exposed                     | 3 / 6848 (0.04%)  | 0 / 3424 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Thermal Burn                                    |                   |                   |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 6848 (0.03%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tibia Fracture                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 2 / 3424 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Toxicity To Various Agents                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tracheal Injury                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Traumatic Brain Injury                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Traumatic Intracranial Haemorrhage              |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Upper Limb Fracture                             |                  |                  |  |
| subjects affected / exposed                     | 3 / 6848 (0.04%) | 2 / 3424 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Congenital, familial and genetic disorders      |                  |                  |  |
| Cryptorchism                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Duchenne Muscular Dystrophy                     |                  |                  |  |



|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Familial Periodic Paralysis</b>              |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Fibrous Dysplasia Of Bone</b>                |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Odontogenic Cyst</b>                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Phimosis</b>                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 2 / 3424 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Cardiac disorders</b>                        |                  |                  |  |
| <b>Cardiac Failure Congestive</b>               |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Cardiogenic Shock</b>                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| <b>Rheumatic Heart Disease</b>                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| <b>Supraventricular Tachycardia</b>             |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ventricular Tachycardia                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nervous system disorders                        |                  |                  |  |
| Acute Disseminated Encephalomyelitis            |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Autonomic Neuropathy                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Cerebral Venous Thrombosis                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Complex Partial Seizures                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Convulsion                                      |                  |                  |  |
| subjects affected / exposed                     | 4 / 6848 (0.06%) | 2 / 3424 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Convulsions Local                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Encephalitis                                    |                  |                  |  |

|                                                 |                   |                  |  |
|-------------------------------------------------|-------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6848 (0.00%)  | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1            |  |
| Epilepsy                                        |                   |                  |  |
| subjects affected / exposed                     | 8 / 6848 (0.12%)  | 4 / 3424 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 9             | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Extrapyramidal Disorder                         |                   |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%)  | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Febrile Convulsion                              |                   |                  |  |
| subjects affected / exposed                     | 13 / 6848 (0.19%) | 7 / 3424 (0.20%) |  |
| occurrences causally related to treatment / all | 0 / 23            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Grand Mal Convulsion                            |                   |                  |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%)  | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Guillain-Barre Syndrome                         |                   |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Intercostal Neuralgia                           |                   |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%)  | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Ischaemic Stroke                                |                   |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Migraine Without Aura                           |                   |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Partial Seizures                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Presyncope                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Status Epilepticus                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Syncope                                         |                  |                  |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tension Headache                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tonic Convulsion                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Viith Nerve Paralysis                           |                  |                  |  |
| subjects affected / exposed                     | 3 / 6848 (0.04%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Blood and lymphatic system disorders            |                  |                  |  |
| Anaemia                                         |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anaemia Of Pregnancy                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemorrhagic Anaemia                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Iron Deficiency Anaemia                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lymphadenitis                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ear and labyrinth disorders                     |                  |                  |  |
| Middle Ear Effusion                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vertigo Positional                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vestibular Disorder                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Eye disorders                                   |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| Chalazion                                       |                  |                  |  |
| subjects affected / exposed                     | 3 / 6848 (0.04%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Choroidal Dystrophy                             |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Corneal Oedema                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal disorders                      |                  |                  |  |
| Abdominal Pain                                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal Pain Lower                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal Pain Upper                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anal Fistula                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Caecitis                                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colitis                                         |                  |                  |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 2 / 6848 (0.03%)  | 0 / 3424 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Dental Caries                                   |                   |                   |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%)  | 0 / 3424 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Diarrhoea                                       |                   |                   |  |
| subjects affected / exposed                     | 6 / 6848 (0.09%)  | 6 / 3424 (0.18%)  |  |
| occurrences causally related to treatment / all | 0 / 6             | 0 / 6             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Dyspepsia                                       |                   |                   |  |
| subjects affected / exposed                     | 8 / 6848 (0.12%)  | 2 / 3424 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 8             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Enteritis                                       |                   |                   |  |
| subjects affected / exposed                     | 5 / 6848 (0.07%)  | 1 / 3424 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 5             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Enterocolitis                                   |                   |                   |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%)  | 0 / 3424 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Food Poisoning                                  |                   |                   |  |
| subjects affected / exposed                     | 9 / 6848 (0.13%)  | 3 / 3424 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 9             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Gastritis                                       |                   |                   |  |
| subjects affected / exposed                     | 31 / 6848 (0.45%) | 14 / 3424 (0.41%) |  |
| occurrences causally related to treatment / all | 0 / 32            | 0 / 16            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Gastrointestinal Disorder                       |                   |                   |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 9 / 6848 (0.13%) | 5 / 3424 (0.15%) |  |
| occurrences causally related to treatment / all | 0 / 10           | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal Haemorrhage                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal Inflammation                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrooesophageal Reflux Disease                |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemorrhoids                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ileus                                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Inguinal Hernia                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mouth Cyst                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancreatitis Acute                              |                  |                  |  |



|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pancreatitis Chronic                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Periodontitis                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Peritonitis                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Salivary Gland Calculus                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Salivary Gland Mucocoele                        |                  |                  |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tooth Development Disorder                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Tooth Impacted                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Toothache                                       |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skin and subcutaneous tissue disorders          |                  |                  |  |
| Angioedema                                      |                  |                  |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Dermal Cyst                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Henoch-Schonlein Purpura                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Skin Hypertrophy                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urticaria                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 2 / 3424 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal and urinary disorders                     |                  |                  |  |
| Calculus Ureteric                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Glomerulonephritis Acute                        |                  |                  |  |
| subjects affected / exposed                     | 3 / 6848 (0.04%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nephrotic Syndrome                              |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 6848 (0.03%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neurogenic Bladder                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Post Streptococcal Glomerulonephritis           |                  |                  |  |
| subjects affected / exposed                     | 9 / 6848 (0.13%) | 3 / 3424 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal Failure Acute                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal Tubular Acidosis                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Endocrine disorders                             |                  |                  |  |
| Goitre                                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Musculoskeletal and connective tissue disorders |                  |                  |  |
| Bone Cyst                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Exostosis                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| Fasciitis                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Fracture Malunion                               |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Jaw Cyst                                        |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Muscle Spasms                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Myositis                                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rheumatic Fever                                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Synovial Cyst                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Synovitis                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infections and infestations                     |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| Abscess Limb                                    |                  |                  |  |
| subjects affected / exposed                     | 4 / 6848 (0.06%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abscess Neck                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abscess Of External Auditory Meatus             |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Acinetobacter Bacteraemia                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Acute Sinusitis                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Acute Tonsillitis                               |                  |                  |  |
| subjects affected / exposed                     | 7 / 6848 (0.10%) | 2 / 3424 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Adenoiditis                                     |                  |                  |  |
| subjects affected / exposed                     | 4 / 6848 (0.06%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Amoebiasis                                      |                  |                  |  |
| subjects affected / exposed                     | 9 / 6848 (0.13%) | 4 / 3424 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Amoebic Dysentery                               |                  |                  |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 3 / 6848 (0.04%)  | 2 / 3424 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Anal Abscess                                    |                   |                   |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%)  | 2 / 3424 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Appendiceal Abscess                             |                   |                   |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%)  | 1 / 3424 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Appendicitis                                    |                   |                   |  |
| subjects affected / exposed                     | 33 / 6848 (0.48%) | 27 / 3424 (0.79%) |  |
| occurrences causally related to treatment / all | 0 / 33            | 0 / 27            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Appendicitis Perforated                         |                   |                   |  |
| subjects affected / exposed                     | 5 / 6848 (0.07%)  | 4 / 3424 (0.12%)  |  |
| occurrences causally related to treatment / all | 0 / 5             | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bacterial Diarrhoea                             |                   |                   |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 0 / 3424 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bacterial Infection                             |                   |                   |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%)  | 1 / 3424 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bartholin's Abscess                             |                   |                   |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%)  | 0 / 3424 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Bronchiolitis                                   |                   |                   |  |

|                                                 |                   |                  |  |
|-------------------------------------------------|-------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Bronchitis                                      |                   |                  |  |
| subjects affected / exposed                     | 16 / 6848 (0.23%) | 6 / 3424 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 16            | 0 / 8            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Bronchitis Bacterial                            |                   |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Bronchopneumonia                                |                   |                  |  |
| subjects affected / exposed                     | 8 / 6848 (0.12%)  | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 8             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Brucellosis                                     |                   |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Cellulitis                                      |                   |                  |  |
| subjects affected / exposed                     | 7 / 6848 (0.10%)  | 3 / 3424 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 7             | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Chikungunya Virus Infection                     |                   |                  |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%)  | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Chronic Tonsillitis                             |                   |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Conjunctivitis Infective                        |                   |                  |  |

|                                                 |                    |                    |  |
|-------------------------------------------------|--------------------|--------------------|--|
| subjects affected / exposed                     | 1 / 6848 (0.01%)   | 0 / 3424 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 1              | 0 / 0              |  |
| deaths causally related to treatment / all      | 0 / 0              | 0 / 0              |  |
| Cystitis                                        |                    |                    |  |
| subjects affected / exposed                     | 3 / 6848 (0.04%)   | 0 / 3424 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 3              | 0 / 0              |  |
| deaths causally related to treatment / all      | 0 / 0              | 0 / 0              |  |
| Dengue Fever                                    |                    |                    |  |
| subjects affected / exposed                     | 238 / 6848 (3.48%) | 158 / 3424 (4.61%) |  |
| occurrences causally related to treatment / all | 0 / 241            | 0 / 167            |  |
| deaths causally related to treatment / all      | 0 / 0              | 0 / 0              |  |
| Diarrhoea Infectious                            |                    |                    |  |
| subjects affected / exposed                     | 3 / 6848 (0.04%)   | 5 / 3424 (0.15%)   |  |
| occurrences causally related to treatment / all | 0 / 3              | 0 / 5              |  |
| deaths causally related to treatment / all      | 0 / 0              | 0 / 0              |  |
| Disseminated Tuberculosis                       |                    |                    |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%)   | 0 / 3424 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 1              | 0 / 0              |  |
| deaths causally related to treatment / all      | 0 / 0              | 0 / 0              |  |
| Encephalitis Viral                              |                    |                    |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%)   | 1 / 3424 (0.03%)   |  |
| occurrences causally related to treatment / all | 0 / 0              | 0 / 1              |  |
| deaths causally related to treatment / all      | 0 / 0              | 0 / 0              |  |
| Endophthalmitis                                 |                    |                    |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%)   | 1 / 3424 (0.03%)   |  |
| occurrences causally related to treatment / all | 0 / 0              | 0 / 1              |  |
| deaths causally related to treatment / all      | 0 / 0              | 0 / 0              |  |
| Furuncle                                        |                    |                    |  |
| subjects affected / exposed                     | 3 / 6848 (0.04%)   | 0 / 3424 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 3              | 0 / 0              |  |
| deaths causally related to treatment / all      | 0 / 0              | 0 / 0              |  |
| Gastritis Bacterial                             |                    |                    |  |



|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 2 / 6848 (0.03%)  | 0 / 3424 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Gastroenteritis                                 |                   |                   |  |
| subjects affected / exposed                     | 53 / 6848 (0.77%) | 40 / 3424 (1.17%) |  |
| occurrences causally related to treatment / all | 0 / 64            | 0 / 43            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Gastroenteritis Bacterial                       |                   |                   |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 1 / 3424 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Gastroenteritis Viral                           |                   |                   |  |
| subjects affected / exposed                     | 3 / 6848 (0.04%)  | 1 / 3424 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Gastrointestinal Bacterial Infection            |                   |                   |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%)  | 0 / 3424 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Gastrointestinal Infection                      |                   |                   |  |
| subjects affected / exposed                     | 6 / 6848 (0.09%)  | 5 / 3424 (0.15%)  |  |
| occurrences causally related to treatment / all | 0 / 6             | 0 / 5             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Groin Abscess                                   |                   |                   |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%)  | 0 / 3424 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hiv Infection                                   |                   |                   |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 0 / 3424 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Hand-Foot-And-Mouth Disease                     |                   |                   |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 6848 (0.03%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatitis A                                     |                  |                  |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hepatitis Viral                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Herpangina                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Herpes Zoster                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hordeolum                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Infection In An Immunocompromised Host          |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Influenza                                       |                  |                  |  |
| subjects affected / exposed                     | 9 / 6848 (0.13%) | 3 / 3424 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 9            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Leptospirosis                                   |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lobar Pneumonia                                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lymphadenitis Bacterial                         |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Malaria                                         |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Measles                                         |                  |                  |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Meningitis                                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Meningitis Aseptic                              |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Meningitis Bacterial                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mumps                                           |                  |                  |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Nasopharyngitis                                 |                  |                  |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oral Herpes                                     |                  |                  |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Orchitis                                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Otitis Externa                                  |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Otitis Media                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Otitis Media Chronic                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Paratyphoid Fever                               |                  |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Parotitis                                       |                  |                  |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 0 / 3424 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Periorbital Cellulitis                          |                   |                   |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%)  | 1 / 3424 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Peritonsillar Abscess                           |                   |                   |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 0 / 3424 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pharyngitis                                     |                   |                   |  |
| subjects affected / exposed                     | 32 / 6848 (0.47%) | 19 / 3424 (0.55%) |  |
| occurrences causally related to treatment / all | 0 / 35            | 0 / 25            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pharyngitis Bacterial                           |                   |                   |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 0 / 3424 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pharyngitis Streptococcal                       |                   |                   |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 0 / 3424 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pharyngotonsillitis                             |                   |                   |  |
| subjects affected / exposed                     | 15 / 6848 (0.22%) | 4 / 3424 (0.12%)  |  |
| occurrences causally related to treatment / all | 0 / 15            | 0 / 4             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Plasmodium Falciparum Infection                 |                   |                   |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%)  | 1 / 3424 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pneumonia                                       |                   |                   |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 33 / 6848 (0.48%) | 12 / 3424 (0.35%) |  |
| occurrences causally related to treatment / all | 0 / 37            | 0 / 12            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pneumonia Bacterial                             |                   |                   |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 1 / 3424 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pneumonia Measles                               |                   |                   |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%)  | 1 / 3424 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pneumonia Primary Atypical                      |                   |                   |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%)  | 2 / 3424 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pneumonia Viral                                 |                   |                   |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 1 / 3424 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Postoperative Wound Infection                   |                   |                   |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 1 / 3424 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pulmonary Tuberculosis                          |                   |                   |  |
| subjects affected / exposed                     | 5 / 6848 (0.07%)  | 2 / 3424 (0.06%)  |  |
| occurrences causally related to treatment / all | 0 / 5             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pyelonephritis                                  |                   |                   |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 0 / 3424 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Pyelonephritis Acute                            |                   |                   |  |

|                                                 |                   |                  |  |
|-------------------------------------------------|-------------------|------------------|--|
| subjects affected / exposed                     | 4 / 6848 (0.06%)  | 3 / 3424 (0.09%) |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Respiratory Tract Infection                     |                   |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%)  | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Scarlet Fever                                   |                   |                  |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%)  | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Sepsis                                          |                   |                  |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%)  | 2 / 3424 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 1            |  |
| Sinusitis                                       |                   |                  |  |
| subjects affected / exposed                     | 4 / 6848 (0.06%)  | 2 / 3424 (0.06%) |  |
| occurrences causally related to treatment / all | 0 / 4             | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Staphylococcal Sepsis                           |                   |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%)  | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Streptococcal Infection                         |                   |                  |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 0 / 3424 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Tonsillitis                                     |                   |                  |  |
| subjects affected / exposed                     | 12 / 6848 (0.18%) | 4 / 3424 (0.12%) |  |
| occurrences causally related to treatment / all | 0 / 12            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Tonsillitis Bacterial                           |                   |                  |  |

|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 2 / 6848 (0.03%)  | 1 / 3424 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Tooth Abscess                                   |                   |                   |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 0 / 3424 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Tuberculosis                                    |                   |                   |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 1 / 3424 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Tuberculous Pleurisy                            |                   |                   |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%)  | 1 / 3424 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Typhoid Fever                                   |                   |                   |  |
| subjects affected / exposed                     | 15 / 6848 (0.22%) | 13 / 3424 (0.38%) |  |
| occurrences causally related to treatment / all | 0 / 18            | 0 / 13            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Typhus                                          |                   |                   |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%)  | 1 / 3424 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Upper Respiratory Tract Infection               |                   |                   |  |
| subjects affected / exposed                     | 11 / 6848 (0.16%) | 5 / 3424 (0.15%)  |  |
| occurrences causally related to treatment / all | 0 / 11            | 0 / 6             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Urethritis                                      |                   |                   |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 0 / 3424 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Urinary Tract Infection                         |                   |                   |  |



|                                                 |                   |                   |  |
|-------------------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed                     | 22 / 6848 (0.32%) | 14 / 3424 (0.41%) |  |
| occurrences causally related to treatment / all | 0 / 23            | 0 / 17            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Varicella                                       |                   |                   |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 1 / 3424 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Viral Infection                                 |                   |                   |  |
| subjects affected / exposed                     | 32 / 6848 (0.47%) | 29 / 3424 (0.85%) |  |
| occurrences causally related to treatment / all | 0 / 35            | 0 / 29            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Viral Pharyngitis                               |                   |                   |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 1 / 3424 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Viral Rash                                      |                   |                   |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%)  | 3 / 3424 (0.09%)  |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Viral Upper Respiratory Tract Infection         |                   |                   |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%)  | 1 / 3424 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Vulval Abscess                                  |                   |                   |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 0 / 3424 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Wound Infection                                 |                   |                   |  |
| subjects affected / exposed                     | 1 / 6848 (0.01%)  | 1 / 3424 (0.03%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Metabolism and nutrition disorders              |                   |                   |  |
| Calcium Deficiency                              |                   |                   |  |

|                                                 |                  |                  |  |
|-------------------------------------------------|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 6848 (0.01%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypocalcaemia                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 6848 (0.00%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypoglycaemia                                   |                  |                  |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypokalaemia                                    |                  |                  |  |
| subjects affected / exposed                     | 2 / 6848 (0.03%) | 1 / 3424 (0.03%) |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |

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

| <b>Non-serious adverse events</b>                     | CYD Dengue Vaccine Group | Placebo Group       |  |
|-------------------------------------------------------|--------------------------|---------------------|--|
| Total subjects affected by non-serious adverse events |                          |                     |  |
| subjects affected / exposed                           | 942 / 6848 (13.76%)      | 453 / 3424 (13.23%) |  |
| Nervous system disorders                              |                          |                     |  |
| Headache                                              |                          |                     |  |
| subjects affected / exposed <sup>[1]</sup>            | 567 / 1334 (42.50%)      | 264 / 663 (39.82%)  |  |
| occurrences (all)                                     | 866                      | 409                 |  |
| General disorders and administration site conditions  |                          |                     |  |
| Asthenia                                              |                          |                     |  |
| subjects affected / exposed <sup>[2]</sup>            | 378 / 1334 (28.34%)      | 167 / 663 (25.19%)  |  |
| occurrences (all)                                     | 530                      | 244                 |  |
| Injection Site Erythema                               |                          |                     |  |
| subjects affected / exposed <sup>[3]</sup>            | 107 / 1334 (8.02%)       | 52 / 663 (7.84%)    |  |
| occurrences (all)                                     | 142                      | 71                  |  |
| Injection Site Pain                                   |                          |                     |  |

|                                                 |                     |                    |  |
|-------------------------------------------------|---------------------|--------------------|--|
| subjects affected / exposed <sup>[4]</sup>      | 616 / 1334 (46.18%) | 275 / 663 (41.48%) |  |
| occurrences (all)                               | 994                 | 449                |  |
| Injection Site Swelling                         |                     |                    |  |
| subjects affected / exposed <sup>[5]</sup>      | 68 / 1334 (5.10%)   | 33 / 663 (4.98%)   |  |
| occurrences (all)                               | 84                  | 36                 |  |
| Malaise                                         |                     |                    |  |
| subjects affected / exposed <sup>[6]</sup>      | 476 / 1334 (35.68%) | 239 / 663 (36.05%) |  |
| occurrences (all)                               | 689                 | 352                |  |
| Pyrexia                                         |                     |                    |  |
| subjects affected / exposed <sup>[7]</sup>      | 267 / 1334 (20.01%) | 125 / 663 (18.85%) |  |
| occurrences (all)                               | 291                 | 137                |  |
| Respiratory, thoracic and mediastinal disorders |                     |                    |  |
| Cough                                           |                     |                    |  |
| subjects affected / exposed <sup>[8]</sup>      | 63 / 1334 (4.72%)   | 48 / 663 (7.24%)   |  |
| occurrences (all)                               | 69                  | 61                 |  |
| Rhinorrhoea                                     |                     |                    |  |
| subjects affected / exposed <sup>[9]</sup>      | 46 / 1334 (3.45%)   | 36 / 663 (5.43%)   |  |
| occurrences (all)                               | 48                  | 43                 |  |
| Musculoskeletal and connective tissue disorders |                     |                    |  |
| Myalgia                                         |                     |                    |  |
| subjects affected / exposed <sup>[10]</sup>     | 414 / 1334 (31.03%) | 197 / 663 (29.71%) |  |
| occurrences (all)                               | 585                 | 296                |  |
| Infections and infestations                     |                     |                    |  |
| Nasopharyngitis                                 |                     |                    |  |
| subjects affected / exposed <sup>[11]</sup>     | 85 / 1334 (6.37%)   | 45 / 663 (6.79%)   |  |
| occurrences (all)                               | 113                 | 61                 |  |
| Upper Respiratory Tract Infection               |                     |                    |  |
| subjects affected / exposed <sup>[12]</sup>     | 95 / 1334 (7.12%)   | 54 / 663 (8.14%)   |  |
| occurrences (all)                               | 104                 | 62                 |  |

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Non-serious adverse events were assessed in a subset of subjects in each group, in accordance with the protocol.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Non-serious adverse events were assessed in a subset of subjects in each group, in accordance with the protocol.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Non-serious adverse events were assessed in a subset of subjects in each group, in accordance with the protocol.

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Non-serious adverse events were assessed in a subset of subjects in each group, in accordance with the protocol.

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Non-serious adverse events were assessed in a subset of subjects in each group, in accordance with the protocol.

[6] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Non-serious adverse events were assessed in a subset of subjects in each group, in accordance with the protocol.

[7] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Non-serious adverse events were assessed in a subset of subjects in each group, in accordance with the protocol.

[8] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Non-serious adverse events were assessed in a subset of subjects in each group, in accordance with the protocol.

[9] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Non-serious adverse events were assessed in a subset of subjects in each group, in accordance with the protocol.

[10] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Non-serious adverse events were assessed in a subset of subjects in each group, in accordance with the protocol.

[11] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Non-serious adverse events were assessed in a subset of subjects in each group, in accordance with the protocol.

[12] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: Non-serious adverse events were assessed in a subset of subjects in each group, in accordance with the protocol.

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
|-----------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 21 January 2011 | The 'Other Objectives' section was revised to improve specificity of confirmation of dengue in line with the non-primary endpoint suggested in the WHO guidelines (version 2.0); It was also specified that the safety surveillance will be conducted by the Principal Investigators.                                                                                                                                                                                                                                                                      |
| 03 August 2011  | Clarified the issue of sample collection times and the reporting period; Extended the collection of all SAEs to the entire study period; Noted that laboratory staff is blinded to treatment allocation and also the stratification by age as (2 to 5 years, 6 to 11 years, and 12 to 14 years); and updated the time window for assessment of serious viscerotropic disease in-line with the update of the Guidelines for Assessing Viscerotropic and Neurotropic Adverse Events, and introduced the use of the WHO Verbal Autopsy Questionnaire.         |
| 29 May 2013     | Modified the testing algorithm for the virological-confirmation by adding the dengue screen RT-PCR and the Simplexa RT-PCR, assessment of the CYD dengue vaccine in preventing symptomatic virologically-confirmed dengue cases; The study objectives was revised along with the addition of 'Other Objectives'; The Hospital Phase was extended by 2 years to allow a 5-year follow-up period after the last vaccination; and the addition of use of neutralization antibody assays and analyses in addition to PRNT to characterize the immune response. |
| 25 January 2015 | Enhanced the surveillance system also known as the Surveillance Expansion Phase (SEP). The subjects who consented to SEP were actively followed for dengue case detection, and an additional visit (Vse) and blood sample at SEP requested. The trial objectives were modified to add other objectives and endpoints; to describe the occurrence of hospitalized VCD cases and severe VCD throughout SEP and entire trial duration and correlate immunogenicity profile as assessed by PRNT at post-dose 3 and/or at the time of SEP enrollment            |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/25018116>

<http://www.ncbi.nlm.nih.gov/pubmed/26614588>

<http://www.ncbi.nlm.nih.gov/pubmed/26214039>

<http://www.ncbi.nlm.nih.gov/pubmed/26639777>

<http://www.ncbi.nlm.nih.gov/pubmed/27007959>

<http://www.ncbi.nlm.nih.gov/pubmed/27414655>