



## Clinical trial results:

### International Randomized Double Blind Study Evaluating the Efficacy and the Safety of Clopidogrel 0.2 mg/kg Once Daily Versus Placebo in Neonates and Infants With Cyanotic Congenital Heart Disease Palliated With Systemic to Pulmonary Artery Shunt

#### Summary

|                          |   |
|--------------------------|---|
| EudraCT number           | 2006-000946-38                                  |
| Trial protocol           | BE GB DE FI SE DK PT FR HU IT NL Outside EU/EEA |
| Global end of trial date | 01 February 2010                                |

#### Results information

|                                |              |
|--------------------------------|--------------|
| Result version number          | v1 (current) |
| This version publication date  | 23 May 2016  |
| First version publication date | 16 May 2015  |

#### Trial information

##### Trial identification

|                       |         |
|-----------------------|---------|
| Sponsor protocol code | EFC5314 |
|-----------------------|---------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT00396877 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Sanofi aventis recherche & developpement   |
| Sponsor organisation address | 1 avenue Pierre Brossolette, Chilly-Mazarin , France, 91380                              |
| Public contact               | Trial transparency team, Sanofi aventis recherche & developpement, Contact-US@sanofi.com |
| Scientific contact           | Trial transparency team, Sanofi aventis recherche & developpement, 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-000049-PIP01-07 |
| 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                       | 26 February 2010 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 01 February 2010 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the efficacy of Clopidogrel 0.2 mg/kg/day for the reduction of all cause mortality and shunt related morbidity in neonates or infants with cyanotic congenital heart disease palliated with a systemic-to-pulmonary artery shunt (e.g. modified Blalock Taussig Shunt [BTS]).

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of pediatric subjects. The parent(s) or guardian(s) as well as the children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child-appropriate language was provided and explained to the child. Repeated invasive procedures were minimized. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anesthesia may have been used to minimize distress and discomfort.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 03 November 2006 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Argentina: 52          |
| Country: Number of subjects enrolled | Brazil: 65             |
| Country: Number of subjects enrolled | Netherlands: 6         |
| Country: Number of subjects enrolled | Norway: 16             |
| Country: Number of subjects enrolled | Portugal: 20           |
| Country: Number of subjects enrolled | Israel: 7              |
| Country: Number of subjects enrolled | Mexico: 69             |
| Country: Number of subjects enrolled | Poland: 10             |
| Country: Number of subjects enrolled | Russian Federation: 28 |
| Country: Number of subjects enrolled | Singapore: 4           |
| Country: Number of subjects enrolled | South Africa: 26       |
| Country: Number of subjects enrolled | Taiwan: 22             |
| Country: Number of subjects enrolled | Sweden: 11             |
| Country: Number of subjects enrolled | Egypt: 10              |
| Country: Number of subjects enrolled | Finland: 3             |
| Country: Number of subjects enrolled | Germany: 113           |
| Country: Number of subjects enrolled | Belgium: 21            |

|                                      |                       |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Canada: 11            |
| Country: Number of subjects enrolled | China: 21             |
| Country: Number of subjects enrolled | Denmark: 6            |
| Country: Number of subjects enrolled | France: 21            |
| Country: Number of subjects enrolled | Italy: 39             |
| Country: Number of subjects enrolled | Hong Kong: 1          |
| Country: Number of subjects enrolled | Hungary: 18           |
| Country: Number of subjects enrolled | India: 47             |
| Country: Number of subjects enrolled | Korea, Republic of: 5 |
| Country: Number of subjects enrolled | Malaysia: 9           |
| Country: Number of subjects enrolled | Spain: 30             |
| Country: Number of subjects enrolled | Thailand: 5           |
| Country: Number of subjects enrolled | United Kingdom: 32    |
| Country: Number of subjects enrolled | United States: 178    |
| Worldwide total number of subjects   | 906                   |
| EEA total number of subjects         | 346                   |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 404 |
| Infants and toddlers (28 days-23 months)  | 502 |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 0   |
| From 65 to 84 years                       | 0   |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Recruitment was initially planned with a minimum of 490 subjects anticipating that it would continue until a total of 172 subjects reaching primary endpoint criteria is achieved. Finally 906 subjects were enrolled and randomized between November 2006 and October 2009 in 134 sites in 31 countries. Actual median follow-up was 5.8 months.

### Pre-assignment

Screening details:

A subject was considered randomized when informed consent had been obtained and there was confirmation of successful allocation of a randomization number through the study treatment allocation system (Interactive Voice Response System).

### Period 1

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

Blinding implementation details:

Eligible subjects were randomized to receive either Clopidogrel or placebo in a 1:1 ration without the disclosure of assigned treatments to the investigator and to the subject's parents/guardians. Both the Clopidogrel and placebo were reconstituted in the same fashion and were similar in appearance.

### Arms

|                              |         |
|------------------------------|---------|
| Are arms mutually exclusive? | Yes     |
| <b>Arm title</b>             | Placebo |

Arm description:

Clopidogrel matching placebo until primary endpoint criteria was reached i.e. (shunt thrombosis, the next surgical procedure for correction of the congenital heart disease or death) or one year of age or common study-end-date, whichever came first.

|  |                                      |
|--|--------------------------------------|
| Arm type                               | Placebo                              |
| Investigational medicinal product name | Placebo                              |
| Investigational medicinal product code |                                      |
| Other name                             |                                      |
| Pharmaceutical forms                   | Powder and solvent for oral solution |
| Routes of administration               | Gastroenteral use, Oral use          |

Dosage and administration details:

Placebo to be administered once daily with a graduated syringe in the mouth or via a feeding tube.

|                  |                           |
|------------------|---------------------------|
| <b>Arm title</b> | Clopidogrel 0.2 mg/kg/Day |
|------------------|---------------------------|

Arm description:

Clopidogrel until the primary endpoint criteria was reached i.e. (shunt thrombosis, the next surgical procedure for correction of the congenital heart disease or death) or one year of age or the common study-end-date, whichever came first

|  |                                      |
|--|--------------------------------------|
| Arm type                               | Experimental                         |
| Investigational medicinal product name | Clopidogrel                          |
| Investigational medicinal product code | SR25990                              |
| Other name                             | Plavix                               |
| Pharmaceutical forms                   | Powder and solvent for oral solution |
| Routes of administration               | Gastroenteral use, Oral use          |

Dosage and administration details:

Clopidogrel administered once daily with a graduated syringe in the mouth or via a feeding tube.  
Dose: daily dose adjusted for weight.

| <b>Number of subjects in period 1</b> | Placebo | Clopidogrel 0.2<br>mg/kg/Day |
|---------------------------------------|---------|------------------------------|
| Started                               | 439     | 467                          |
| Treated                               | 436     | 464                          |
| Completed                             | 433     | 459                          |
| Not completed                         | 6       | 8                            |
| Lost to follow-up                     | 2       | 1                            |
| Parent(s)/guardian(s)'s request       | 4       | 7                            |

## Baseline characteristics

### Reporting groups

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

Reporting group description:

Clopidogrel matching placebo until primary endpoint criteria was reached i.e. (shunt thrombosis, the next surgical procedure for correction of the congenital heart disease or death) or one year of age or common study-end-date, whichever came first.

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | Clopidogrel 0.2 mg/kg/Day |
|-----------------------|---------------------------|

Reporting group description:

Clopidogrel until the primary endpoint criteria was reached i.e. (shunt thrombosis, the next surgical procedure for correction of the congenital heart disease or death) or one year of age or the common study-end-date, whichever came first

| Reporting group values | Placebo | Clopidogrel 0.2 mg/kg/Day | Total |
|------------------------|---------|---------------------------|-------|
| Number of subjects     | 439     | 467                       | 906   |
| Age categorical        |         |                           |       |
| Units: Subjects        |         |                           |       |
| ≤ 30 days              | 223     | 238                       | 461   |
| 30 (<) - 92 days       | 216     | 229                       | 445   |
| Age continuous         |         |                           |       |
| Units: days            |         |                           |       |
| arithmetic mean        | 36      | 36.1                      |       |
| standard deviation     | ± 22.5  | ± 22.3                    | -     |
| Gender categorical     |         |                           |       |
| Units: Subjects        |         |                           |       |
| Female                 | 185     | 198                       | 383   |
| Male                   | 254     | 269                       | 523   |
| Region of Enrollment   |         |                           |       |
| Units: Subjects        |         |                           |       |
| United States          | 90      | 88                        | 178   |
| Portugal               | 10      | 10                        | 20    |
| Taiwan                 | 12      | 10                        | 22    |
| Hong Kong              | 1       | 0                         | 1     |
| Thailand               | 2       | 3                         | 5     |
| Spain                  | 16      | 14                        | 30    |
| Israel                 | 3       | 4                         | 7     |
| Russian Federation     | 13      | 15                        | 28    |
| Italy                  | 20      | 19                        | 39    |
| India                  | 20      | 27                        | 47    |
| France                 | 11      | 10                        | 21    |
| Malaysia               | 5       | 4                         | 9     |
| Denmark                | 3       | 3                         | 6     |
| South Africa           | 13      | 13                        | 26    |
| Netherlands            | 2       | 4                         | 6     |
| China                  | 10      | 11                        | 21    |
| Korea, Republic of     | 3       | 2                         | 5     |
| Finland                | 2       | 1                         | 3     |
| United Kingdom         | 16      | 16                        | 32    |
| Egypt                  | 4       | 6                         | 10    |

|   |            |            |     |
|---|------------|------------|-----|
| Hungary   | 9          | 9          | 18  |
| Mexico  | 32         | 37         | 69  |
| Canada  | 5          | 6          | 11  |
| Argentina   | 24         | 28         | 52  |
| Brazil  | 31         | 34         | 65  |
| Belgium   | 9          | 12         | 21  |
| Poland  | 3          | 7          | 10  |
| Singapore   | 2          | 2          | 4   |
| Germany   | 54         | 59         | 113 |
| Norway  | 8          | 8          | 16  |
| Sweden  | 6          | 5          | 11  |
| Type of systemic-to-pulmonary artery shunt palliation   |            |            |     |
| One subject didn't have a systemic-to-pulmonary artery shunt but underwent stenting of the right ventricular outflow track. |            |            |     |
| Units: Subjects   |            |            |     |
| Modified Blalock Taussig Shunt With Norwood   | 51         | 62         | 113 |
| Modified Blalock Taussig Shunt Without Norwood  | 252        | 257        | 509 |
| Sano Procedure With Norwood   | 54         | 60         | 114 |
| Sano Procedure Without Norwood  | 2          | 5          | 7   |
| Central Shunt   | 38         | 40         | 78  |
| Stent of Ductus Arteriosus  | 42         | 42         | 84  |
| Not Applicable  | 0          | 1          | 1   |
| Shunt on cardiopulmonary bypass   |            |            |     |
| Units: Subjects   |            |            |     |
| Yes   | 177        | 194        | 371 |
| No  | 262        | 273        | 535 |
| Time from shunt palliation to randomization   |            |            |     |
| Units: Subjects   |            |            |     |
| less than or equal to ( $\leq$ ) 1 week   | 116        | 113        | 229 |
| 1 (less than [ $<$ ]) to 2 weeks  | 105        | 126        | 231 |
| 2 ( $<$ ) to 4 weeks  | 117        | 119        | 236 |
| greater than ( $>$ ) 4 weeks  | 101        | 109        | 210 |
| Weight  |            |            |     |
| Units: kilograms (kg)   |            |            |     |
| arithmetic mean   | 3.5        | 3.4        |     |
| standard deviation  | $\pm 0.7$  | $\pm 0.7$  | -   |
| Age at shunt palliation   |            |            |     |
| Units: Days   |            |            |     |
| arithmetic mean   | 16         | 16.2       |     |
| standard deviation  | $\pm 18.7$ | $\pm 18.6$ | -   |
| Height  |            |            |     |
| Units: Centimeters (cm)   |            |            |     |
| arithmetic mean   | 51.8       | 51.4       |     |
| standard deviation  | $\pm 4.6$  | $\pm 4.4$  | -   |

## End points

### End points reporting groups

|  |                           |
|--|---------------------------|
| Reporting group title  | Placebo                   |
| Reporting group description:<br>Clopidogrel matching placebo until primary endpoint criteria was reached i.e. (shunt thrombosis, the next surgical procedure for correction of the congenital heart disease or death) or one year of age or common study-end-date, whichever came first. |                           |
| Reporting group title  | Clopidogrel 0.2 mg/kg/Day |
| Reporting group description:<br>Clopidogrel until the primary endpoint criteria was reached i.e. (shunt thrombosis, the next surgical procedure for correction of the congenital heart disease or death) or one year of age or the common study-end-date, whichever came first           |                           |

### Primary: Number of Subjects Reaching Primary Endpoint Criteria (First Occurrence of Death / Shunt Thrombosis / Cardiac Procedure < 120 Days Considered of Thrombotic Nature)

|   |   |
|---|---|
| End point title   | Number of Subjects Reaching Primary Endpoint Criteria (First Occurrence of Death / Shunt Thrombosis / Cardiac Procedure < 120 Days Considered of Thrombotic Nature) |
| End point description:<br>The primary endpoint was the first occurrence of any of the following events: Death (including heart transplant); Shunt thrombosis requiring intervention; Hospitalization for bi-directional Glenn procedure or any cardiac related intervention prior to 120 days of age following an event or a shunt narrowing considered being of thrombotic nature by the blinded adjudication committee. Only the first event was counted. The analysis was performed on the intent-to-treat (ITT) population (i.e. all randomized subjects irrespective of whether or not the subject actually received study drug or the subject's compliance with the study protocol). Subjects were included in the treatment group to which they were originally allocated. |   |
| End point type  | Primary   |
| End point timeframe:<br>Median follow-up of 5.8 months (up to a maximum of 12 months after randomization)   |   |

| End point values                                   | Placebo         | Clopidogrel 0.2 mg/kg/Day |  |  |
|--|-----------------|---------------------------|--|--|
| Subject group type                                 | Reporting group | Reporting group           |  |  |
| Number of subjects analysed                        | 439             | 467                       |  |  |
| Units: Subjects                                    |                 |                           |  |  |
| Death / Shunt Thrombosis / Cardiac Procedure       | 90              | 89                        |  |  |
| - Death  | 60              | 51                        |  |  |
| - Shunt thrombosis                                 | 21              | 26                        |  |  |
| - Cardiac procedure <120 days of thrombotic nature | 9               | 12                        |  |  |

## Statistical analyses



|  |                                       |
|--|---------------------------------------|
| <b>Statistical analysis title</b>  | Clopidogrel 0.2 mg/kg/Day vs. Placebo |
| Statistical analysis description:  |                                       |
| Due to the limited knowledge in this population, 3 interim analyses were performed at approximately 40%, 60%, 80% and 100% of maximum number of 172 required primary efficacy events to evaluate the effect of Clopidogrel on endpoint with potential to end trial in case of a clear efficacy advantage for Clopidogrel. Study was designed with 80% power and an overall type I error rate of 5%. Relative Risk Reduction (Clopidogrel vs placebo) and 95% CI estimated using Cox's proportional hazards model |                                       |
| Comparison groups  | Placebo v Clopidogrel 0.2 mg/kg/Day   |
| Number of subjects included in analysis  | 906                                   |
| Analysis specification   | Pre-specified                         |
| Analysis type  | superiority                           |
| P-value  | = 0.434 <sup>[1]</sup>                |
| Method   | Logrank                               |
| Parameter estimate   | Relative Risk Reduction (%)           |
| Point estimate   | 11.1                                  |
| Confidence interval  |                                       |
| level  | 95 %                                  |
| sides  | 2-sided                               |
| lower limit  | -19.2                                 |
| upper limit  | 33.6                                  |

Notes:

[1] - The a-priori threshold for statistical significance was < 0.035 reflecting the adjustment for interim analyses. No other adjustment for multiplicity was made.

## Secondary: Number of Subjects With Bleeding Events

|                 |   |
|-----------------|---|
| End point title | Number of Subjects With Bleeding Events |
|-----------------|---|

End point description:

Bleeding events spanning from signature of the Informed Consent Form up to the last visit were collected as for any Adverse Event.

The 'on-treatment' period was defined as the period from randomization up until 28 days after treatment discontinuation or final follow-up visit, whichever came first, and subjects who experienced bleeding events during that period were counted. The analysis was performed on the exposed population (i.e. all randomized subjects who received at least one dose of study drug regardless of the amount of treatment received). Subjects were included in the treatment group according to the treatment received.

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

End point timeframe:

From randomization up to 28 days after treatment discontinuation or final follow-up visit, whichever comes first

| End point values                                 | Placebo         | Clopidogrel 0.2 mg/kg/Day |  |  |
|--|-----------------|---------------------------|--|--|
| Subject group type                               | Reporting group | Reporting group           |  |  |
| Number of subjects analysed                      | 436             | 464                       |  |  |
| Units: Subjects                                  |                 |                           |  |  |
| Any bleeding event                               | 88              | 87                        |  |  |
| - Serious  | 32              | 30                        |  |  |
| - Serious with an outcome of death               | 1               | 1                         |  |  |
| - Leading to permanent treatment discontinuation | 9               | 9                         |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of Subjects According to Bleeding Type/Etiology

|                 |  |
|-----------------|--|
| End point title | Number of Subjects According to Bleeding Type/Etiology |
|-----------------|--|

End point description:

For all reported bleeding events, the type and the etiology of the bleeding event were collected. Subjects who experienced bleeding events during the 'on-treatment period' were counted by bleeding type and etiology. Subjects who had multiple bleeding could be counted several times. The analysis was performed on the same population as previously (i.e. exposed population).

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

End point timeframe:

From randomization up to 28 days after treatment discontinuation or final follow-up visit, whichever comes first

| End point values                | Placebo         | Clopidogrel 0.2 mg/kg/Day |  |  |
|---------------------------------|-----------------|---------------------------|--|--|
| Subject group type              | Reporting group | Reporting group           |  |  |
| Number of subjects analysed     | 436             | 464                       |  |  |
| Units: Subjects                 |                 |                           |  |  |
| Spontaneous                     | 60              | 56                        |  |  |
| Post-traumatic                  | 6               | 11                        |  |  |
| Puncture (vascular access site) | 19              | 9                         |  |  |
| Surgical                        | 10              | 17                        |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Adverse Events (AEs) were collected from signature of the informed consent form up to the last visit regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

AEs that developed/worsened and deaths that occurred during 'on treatment period' (from randomization up to 28 days after treatment discontinuation or final follow-up visit, whichever came first) are reported. All-cause deaths include cardiovascular deaths (primary efficacy endpoint) and non-cardiovascular deaths resulting from AEs.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 12.1 |
|--------------------|------|

### Reporting groups

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

Reporting group description:

Clopidogrel matching placebo until primary endpoint criteria was reached i.e. (shunt thrombosis, the next surgical procedure for correction of the congenital heart disease or death) or one year of age or common study-end-date, whichever came first.

|                       |                          |
|-----------------------|--------------------------|
| Reporting group title | Clopidogrel 0.2mg/kg/day |
|-----------------------|--------------------------|

Reporting group description:

Clopidogrel until the primary endpoint criteria was reached i.e. (shunt thrombosis, the next surgical procedure for correction of the congenital heart disease or death) or one year of age or the common study-end-date, whichever came first

| Serious adverse events                            | Placebo            | Clopidogrel<br>0.2mg/kg/day |  |
|---|--------------------|-----------------------------|--|
| Total subjects affected by serious adverse events |                    |                             |  |
| subjects affected / exposed                       | 196 / 436 (44.95%) | 234 / 464 (50.43%)          |  |
| number of deaths (all causes)                     | 56                 | 50                          |  |
| number of deaths resulting from adverse events    |                    |                             |  |
| Vascular disorders                                |                    |                             |  |
| Aortic Stenosis                                   |                    |                             |  |
| subjects affected / exposed                       | 2 / 436 (0.46%)    | 2 / 464 (0.43%)             |  |
| occurrences causally related to treatment / all   | 0 / 2              | 1 / 3                       |  |
| deaths causally related to treatment / all        | 0 / 0              | 0 / 0                       |  |
| Embolism  |                    |                             |  |
| subjects affected / exposed                       | 1 / 436 (0.23%)    | 0 / 464 (0.00%)             |  |
| occurrences causally related to treatment / all   | 0 / 1              | 0 / 0                       |  |
| deaths causally related to treatment / all        | 0 / 0              | 0 / 0                       |  |
| Circulatory Collapse                              |                    |                             |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypotension                                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 436 (0.46%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypovolaemic Shock                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Peripheral Ischaemia                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peripheral Arterial Occlusive Disease           |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Shock   |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular Stenosis                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Venous Thrombosis                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vena Cava Thrombosis                            |                 |                 |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                          | 1 / 436 (0.23%) | 2 / 464 (0.43%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Surgical and medical procedures                      |                 |                 |  |
| Anorectal Operation                                  |                 |                 |  |
| subjects affected / exposed                          | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Ureteroneocystostomy                                 |                 |                 |  |
| subjects affected / exposed                          | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Cardiovascular Event Prophylaxis                     |                 |                 |  |
| subjects affected / exposed                          | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| 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 |                 |                 |  |
| Catheter Thrombosis                                  |                 |                 |  |
| subjects affected / exposed                          | 1 / 436 (0.23%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Catheter Related Complication                        |                 |                 |  |
| subjects affected / exposed                          | 1 / 436 (0.23%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Catheter Site Haemorrhage                            |                 |                 |  |
| subjects affected / exposed                          | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Feeling Abnormal                                     |                 |                 |  |
| subjects affected / exposed                          | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| General Physical Health Deterioration           |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Puncture Site Haemorrhage                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 436 (0.46%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Irritability                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pyrexia   |                 |                 |  |
| subjects affected / exposed                     | 3 / 436 (0.69%) | 5 / 464 (1.08%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vessel Puncture Site Haematoma                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Immune system disorders                         |                 |                 |  |
| Hypogammaglobulinaemia                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Milk Allergy                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Acute Respiratory Distress Syndrome             |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Apnoea  |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Aspiration                                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 436 (0.46%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Atelectasis                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 2 / 464 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchostenosis                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cough   |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chylothorax                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Diaphragmatic Paralysis                         |                 |                 |  |
| subjects affected / exposed                     | 2 / 436 (0.46%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dyspnoea  |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 2 / 464 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dyspnoea Exertional                             |                 |                 |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 436 (0.00%)  | 1 / 464 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemothorax                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 436 (0.23%)  | 0 / 464 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemoptysis                                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 436 (0.23%)  | 0 / 464 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Hypoxia   |                  |                  |  |
| subjects affected / exposed                     | 11 / 436 (2.52%) | 14 / 464 (3.02%) |  |
| occurrences causally related to treatment / all | 0 / 11           | 0 / 16           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Laryngeal Oedema                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 436 (0.23%)  | 0 / 464 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Laryngeal Stenosis                              |                  |                  |  |
| subjects affected / exposed                     | 1 / 436 (0.23%)  | 1 / 464 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Mediastinal Haematoma                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 436 (0.23%)  | 0 / 464 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Obstructive Airways Disorder                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 436 (0.00%)  | 1 / 464 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mediastinal Haemorrhage                         |                  |                  |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pleural Effusion                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia Aspiration                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Pneumothorax                                    |                 |                 |  |
| subjects affected / exposed                     | 2 / 436 (0.46%) | 2 / 464 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary Artery Stenosis                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 436 (0.46%) | 3 / 464 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary Congestion                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary Embolism                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary Haemorrhage                           |                 |                 |  |
| subjects affected / exposed                     | 2 / 436 (0.46%) | 3 / 464 (0.65%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 3 / 3           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| Pulmonary Vein Occlusion                        |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary Hypertension                          |                 |                 |  |
| subjects affected / exposed                     | 2 / 436 (0.46%) | 2 / 464 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary Vein Stenosis                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary Oedema                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory Arrest                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory Distress                            |                 |                 |  |
| subjects affected / exposed                     | 3 / 436 (0.69%) | 5 / 464 (1.08%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 7           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory Failure                             |                 |                 |  |
| subjects affected / exposed                     | 4 / 436 (0.92%) | 5 / 464 (1.08%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 7           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory Fatigue                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tachypnoea                                      |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 436 (0.46%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Stridor   |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tracheal Stenosis                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tracheomalacia                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper Respiratory Tract Congestion              |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vocal Cord Thickening                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Psychiatric disorders                           |                 |                 |  |
| Agitation                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Aspiration Bronchial                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood Urine Present                             |                 |                 |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 436 (0.23%)  | 0 / 464 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oxygen Saturation Decreased                     |                  |                  |  |
| subjects affected / exposed                     | 10 / 436 (2.29%) | 11 / 464 (2.37%) |  |
| occurrences causally related to treatment / all | 0 / 15           | 0 / 13           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Oxygen Saturation Increased                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 436 (0.23%)  | 0 / 464 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pulmonary Arterial Pressure Decreased           |                  |                  |  |
| subjects affected / exposed                     | 0 / 436 (0.00%)  | 1 / 464 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Platelet Count Decreased                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 436 (0.23%)  | 0 / 464 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pulmonary Arterial Pressure Increased           |                  |                  |  |
| subjects affected / exposed                     | 1 / 436 (0.23%)  | 0 / 464 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Weight Increased                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 436 (0.00%)  | 1 / 464 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Injury, poisoning and procedural complications  |                  |                  |  |
| Accidental Overdose                             |                  |                  |  |
| subjects affected / exposed                     | 2 / 436 (0.46%)  | 3 / 464 (0.65%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Device Breakage                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Drug Toxicity                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (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                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Feeding Tube Complication                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Incisional Hernia                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Graft Thrombosis                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Operative Haemorrhage                           |                 |                 |  |
| subjects affected / exposed                     | 3 / 436 (0.69%) | 3 / 464 (0.65%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| Pneumothorax Traumatic                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Post Procedural Haematoma                       |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Post Procedural Haemorrhage                     |                 |                 |  |
| subjects affected / exposed                     | 4 / 436 (0.92%) | 8 / 464 (1.72%) |  |
| occurrences causally related to treatment / all | 1 / 4           | 6 / 8           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Post Vaccination Syndrome                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Postoperative Fever                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Postoperative Respiratory Distress              |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Postoperative Wound Complication                |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Procedural Complication                         |                 |                 |  |
| subjects affected / exposed                     | 2 / 436 (0.46%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Procedural Site Reaction                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Seroma  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Shunt Blood Flow Excessive                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Shunt Malfunction                               |                 |                 |  |
| subjects affected / exposed                     | 3 / 436 (0.69%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Shunt Occlusion                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skull Fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Shunt Stenosis                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 436 (0.46%) | 2 / 464 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Suture Related Complication                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Suture Rupture                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular Pseudoaneurysm                         |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wound Dehiscence                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Congenital, familial and genetic disorders      |                 |                 |  |
| Atrial Septal Defect                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 2 / 464 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coarctation Of The Aorta                        |                 |                 |  |
| subjects affected / exposed                     | 2 / 436 (0.46%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Laryngomalacia                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Pyloric Stenosis                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary Artery Stenosis Congenital            |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Arrhythmia                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 2 / 464 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Atrioventricular Block                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 2 / 464 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrioventricular Block Complete                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bradycardia                                     |                 |                 |  |
| subjects affected / exposed                     | 4 / 436 (0.92%) | 3 / 464 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac Arrest                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 436 (0.46%) | 3 / 464 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac Disorder                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac Failure                                 |                 |                 |  |
| subjects affected / exposed                     | 5 / 436 (1.15%) | 6 / 464 (1.29%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 7           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac Failure Acute                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac Failure Congestive                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 436 (0.46%) | 4 / 464 (0.86%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac Perforation                             |                 |                 |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Cardio-Respiratory Arrest                       |                 |                  |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 4 / 464 (0.86%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Cardiac Pseudoaneurysm                          |                 |                  |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Cardiogenic Shock                               |                 |                  |  |
| subjects affected / exposed                     | 2 / 436 (0.46%) | 1 / 464 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Cardiopulmonary Failure                         |                 |                  |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Cyanosis  |                 |                  |  |
| subjects affected / exposed                     | 9 / 436 (2.06%) | 24 / 464 (5.17%) |  |
| occurrences causally related to treatment / all | 0 / 9           | 0 / 26           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Dilatation Ventricular                          |                 |                  |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Left Ventricular Dysfunction                    |                 |                  |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Low Cardiac Output Syndrome                     |                 |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 436 (0.46%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nodal Arrhythmia                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pericardial Effusion                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 4 / 464 (0.86%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pericardial Haemorrhage                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary Valve Stenosis                        |                 |                 |  |
| subjects affected / exposed                     | 3 / 436 (0.69%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Right Ventricular Dysfunction                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 2 / 464 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Supraventricular Extrasystoles                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Right Ventricular Failure                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Supraventricular Tachycardia                    |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 436 (0.46%) | 3 / 464 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tachycardia                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tricuspid Valve Incompetence                    |                 |                 |  |
| subjects affected / exposed                     | 3 / 436 (0.69%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ventricular Dysfunction                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ventricular Arrhythmia                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ventricular Fibrillation                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Cerebral Infarction                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 2 / 464 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebral Ischaemia                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 2 / 464 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Clonic Convulsion                               |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Convulsion                                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 436 (0.46%) | 3 / 464 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Convulsions Local                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dyskinesia                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Encephalitis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Embolic Stroke                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| 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                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Hydrocephalus                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Hypoglycaemic Encephalopathy                    |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Ischaemic Stroke                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 3 / 464 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ischaemic Cerebral Infarction                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lethargy  |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 2 / 464 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Partial Seizures                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 3 / 464 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Phrenic Nerve Paralysis                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subarachnoid Haemorrhage Neonatal               |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Poor Sucking Reflex                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vocal Cord Paralysis                            |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vocal Cord Paresis                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| Deficiency Anaemia                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Anaemia   |                 |                 |  |
| subjects affected / exposed                     | 3 / 436 (0.69%) | 2 / 464 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Disseminated Intravascular Coagulation          |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (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 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thrombocytopenia                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 2 / 464 (0.43%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ear and labyrinth disorders                     |                 |                 |  |
| Middle Ear Inflammation                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Gastrointestinal disorders                      |                 |                 |  |
| Abdominal Discomfort                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal Pain                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 2 / 464 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal Pain Upper                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diarrhoea                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 5 / 464 (1.08%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Duodenal Stenosis                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Anal Fissure                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dysphagia                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 436 (0.46%) | 3 / 464 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enterocolitis                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enterocolitis Haemorrhagic                      |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 436 (0.00%) | 2 / 464 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enteritis                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 436 (0.46%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastritis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrooesophageal Reflux Disease                |                 |                 |  |
| subjects affected / exposed                     | 4 / 436 (0.92%) | 6 / 464 (1.29%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 7           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal Haemorrhage                    |                 |                 |  |
| subjects affected / exposed                     | 2 / 436 (0.46%) | 4 / 464 (0.86%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 3 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematemesis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematochezia                                   |                 |                 |  |
| subjects affected / exposed                     | 7 / 436 (1.61%) | 2 / 464 (0.43%) |  |
| occurrences causally related to treatment / all | 4 / 7           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Inguinal Hernia                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intestinal Obstruction                          |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Necrotising Colitis                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 6 / 464 (1.29%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Intestinal Perforation                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lower Gastrointestinal Haemorrhage              |                 |                 |  |
| subjects affected / exposed                     | 3 / 436 (0.69%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 4 / 4           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumatosis Intestinalis                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Post-Tussive Vomiting                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rectal Haemorrhage                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Small Intestinal Obstruction                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vomiting  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 5 / 436 (1.15%) | 5 / 464 (1.08%) |  |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Acute Hepatic Failure                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| 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          |                 |                 |  |
| Dermatitis Allergic                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dermatitis Diaper                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subcutaneous Emphysema                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rash Papular                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Acute Prerenal Failure                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Bladder Prolapse                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| Haematuria                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 436 (0.00%)  | 1 / 464 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Renal Failure                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 436 (0.23%)  | 2 / 464 (0.43%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Vesicoureteric Reflux                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 436 (0.23%)  | 0 / 464 (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                     |                  |                  |  |
| Abdominal Sepsis                                |                  |                  |  |
| subjects affected / exposed                     | 0 / 436 (0.00%)  | 1 / 464 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Adenovirus Infection                            |                  |                  |  |
| subjects affected / exposed                     | 1 / 436 (0.23%)  | 0 / 464 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bacterial Sepsis                                |                  |                  |  |
| subjects affected / exposed                     | 2 / 436 (0.46%)  | 0 / 464 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bacterial Infection                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 436 (0.00%)  | 1 / 464 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bronchiolitis                                   |                  |                  |  |
| subjects affected / exposed                     | 12 / 436 (2.75%) | 15 / 464 (3.23%) |  |
| occurrences causally related to treatment / all | 0 / 13           | 0 / 15           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bronchitis                                      |                  |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 436 (0.23%) | 4 / 464 (0.86%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchitis Bacterial                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchitis Viral                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchopneumonia                                |                 |                 |  |
| subjects affected / exposed                     | 4 / 436 (0.92%) | 4 / 464 (0.86%) |  |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cellulitis                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Catheter Sepsis                                 |                 |                 |  |
| subjects affected / exposed                     | 4 / 436 (0.92%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Candida Sepsis                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Clostridium Difficile Colitis                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 2 / 464 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Endocarditis                                    |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 436 (0.23%) | 4 / 464 (0.86%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ear Infection                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enterococcal Bacteraemia                        |                 |                 |  |
| subjects affected / exposed                     | 2 / 436 (0.46%) | 2 / 464 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enterobacter Sepsis                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enterococcal Infection                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enterococcal Sepsis                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Escherichia Sepsis                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Escherichia Urinary Tract Infection             |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fungal Sepsis                                   |                 |                 |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 436 (0.00%)  | 2 / 464 (0.43%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Gastroenteritis Adenovirus                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 436 (0.23%)  | 1 / 464 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastroenteritis                                 |                  |                  |  |
| subjects affected / exposed                     | 14 / 436 (3.21%) | 24 / 464 (5.17%) |  |
| occurrences causally related to treatment / all | 0 / 15           | 0 / 28           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Gastroenteritis Caliciviral                     |                  |                  |  |
| subjects affected / exposed                     | 1 / 436 (0.23%)  | 0 / 464 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastroenteritis Rotavirus                       |                  |                  |  |
| subjects affected / exposed                     | 3 / 436 (0.69%)  | 2 / 464 (0.43%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Gastrointestinal Infection                      |                  |                  |  |
| subjects affected / exposed                     | 1 / 436 (0.23%)  | 0 / 464 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Gastroenteritis Viral                           |                  |                  |  |
| subjects affected / exposed                     | 4 / 436 (0.92%)  | 5 / 464 (1.08%)  |  |
| occurrences causally related to treatment / all | 0 / 4            | 0 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemophilus Infection                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 436 (0.00%)  | 1 / 464 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Impetigo  |                  |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Incision Site Infection                         |                 |                 |  |
| subjects affected / exposed                     | 2 / 436 (0.46%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Influenza                                       |                 |                 |  |
| subjects affected / exposed                     | 5 / 436 (1.15%) | 6 / 464 (1.29%) |  |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Klebsiella Bacteraemia                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Klebsiella Sepsis                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lobar Pneumonia                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Laryngitis                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Localised Infection                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lower Respiratory Tract Infection               |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 436 (0.46%) | 3 / 464 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lower Respiratory Tract Infection Viral         |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 2 / 464 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung Infection                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 436 (0.46%) | 3 / 464 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mediastinal Abscess                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mediastinitis                                   |                 |                 |  |
| subjects affected / exposed                     | 3 / 436 (0.69%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Meningitis Aseptic                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Meningitis Pneumococcal                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Nosocomial Infection                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 2 / 464 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Otitis Media                                    |                 |                 |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 1 / 436 (0.23%) | 1 / 464 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Otitis Media Acute                              |                 |                  |  |
| subjects affected / exposed                     | 2 / 436 (0.46%) | 0 / 464 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Parainfluenzae Virus Infection                  |                 |                  |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Peritonitis Bacterial                           |                 |                  |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Pneumococcal Sepsis                             |                 |                  |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0            |  |
| Pneumonia                                       |                 |                  |  |
| subjects affected / exposed                     | 9 / 436 (2.06%) | 21 / 464 (4.53%) |  |
| occurrences causally related to treatment / all | 0 / 11          | 0 / 24           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1            |  |
| Pneumonia Bacterial                             |                 |                  |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1            |  |
| Pneumonia Escherichia                           |                 |                  |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Pneumonia Influenzal                            |                 |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia Pneumococcal                          |                 |                 |  |
| subjects affected / exposed                     | 2 / 436 (0.46%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia Respiratory Syncytial Viral           |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 2 / 464 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia Viral                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Post Procedural Cellulitis                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Post Procedural Infection                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 2 / 464 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Postoperative Wound Infection                   |                 |                 |  |
| subjects affected / exposed                     | 2 / 436 (0.46%) | 7 / 464 (1.51%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 7           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pseudomonal Sepsis                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pyelonephritis                                  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 436 (0.46%) | 2 / 464 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary Sepsis                                |                 |                 |  |
| subjects affected / exposed                     | 3 / 436 (0.69%) | 5 / 464 (1.08%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 1           |  |
| Pyelonephritis Acute                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory Syncytial Virus Bronchiolitis       |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 2 / 464 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory Tract Infection                     |                 |                 |  |
| subjects affected / exposed                     | 3 / 436 (0.69%) | 3 / 464 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory Syncytial Virus Infection           |                 |                 |  |
| subjects affected / exposed                     | 3 / 436 (0.69%) | 4 / 464 (0.86%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory Tract Infection Bacterial           |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory Tract Infection Viral               |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 3 / 464 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rhinitis  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rotavirus Infection                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sepsis  |                 |                 |  |
| subjects affected / exposed                     | 4 / 436 (0.92%) | 8 / 464 (1.72%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 8           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 2           |  |
| Sepsis Syndrome                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Septic Shock                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 2 / 464 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin Infection                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 2 / 464 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Staphylococcal Bacteraemia                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Streptococcal Sepsis                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Staphylococcal Sepsis                           |                 |                 |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 436 (0.23%)  | 4 / 464 (0.86%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Upper Respiratory Tract Infection               |                  |                  |  |
| subjects affected / exposed                     | 13 / 436 (2.98%) | 11 / 464 (2.37%) |  |
| occurrences causally related to treatment / all | 0 / 13           | 0 / 11           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urinary Tract Infection                         |                  |                  |  |
| subjects affected / exposed                     | 6 / 436 (1.38%)  | 6 / 464 (1.29%)  |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Viral Diarrhoea                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 436 (0.23%)  | 0 / 464 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Urosepsis                                       |                  |                  |  |
| subjects affected / exposed                     | 1 / 436 (0.23%)  | 2 / 464 (0.43%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Viral Infection                                 |                  |                  |  |
| subjects affected / exposed                     | 6 / 436 (1.38%)  | 7 / 464 (1.51%)  |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 9            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Viral Rash                                      |                  |                  |  |
| subjects affected / exposed                     | 0 / 436 (0.00%)  | 2 / 464 (0.43%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Viral Upper Respiratory Tract Infection         |                  |                  |  |
| subjects affected / exposed                     | 1 / 436 (0.23%)  | 1 / 464 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Wound Abscess                                   |                  |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 436 (0.46%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wound Infection                                 |                 |                 |  |
| subjects affected / exposed                     | 2 / 436 (0.46%) | 3 / 464 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wound Sepsis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Dehydration                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 6 / 464 (1.29%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Failure To Thrive                               |                 |                 |  |
| subjects affected / exposed                     | 6 / 436 (1.38%) | 3 / 464 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 7           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Feeding Disorder Of Infancy Or Early Childhood  |                 |                 |  |
| subjects affected / exposed                     | 5 / 436 (1.15%) | 2 / 464 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Food Intolerance                                |                 |                 |  |
| subjects affected / exposed                     | 3 / 436 (0.69%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperkalaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoglycaemic Seizure                           |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 436 (0.23%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypocalcaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoglycaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 436 (0.23%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoproteinaemia                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyponatraemia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Malnutrition                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 436 (0.00%) | 1 / 464 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolic Acidosis                              |                 |                 |  |
| subjects affected / exposed                     | 2 / 436 (0.46%) | 2 / 464 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Weight Gain Poor                                |                 |                 |  |
| subjects affected / exposed                     | 3 / 436 (0.69%) | 0 / 464 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| 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>                     | Placebo           | Clopidogrel<br>0.2mg/kg/day |  |
|---|-------------------|-----------------------------|--|
| Total subjects affected by non-serious adverse events |                   |                             |  |
| subjects affected / exposed                           | 96 / 436 (22.02%) | 107 / 464 (23.06%)          |  |
| Gastrointestinal disorders                            |                   |                             |  |
| Diarrhoea   |                   |                             |  |
| subjects affected / exposed                           | 20 / 436 (4.59%)  | 24 / 464 (5.17%)            |  |
| occurrences (all)                                     | 26                | 27                          |  |
| Vomiting  |                   |                             |  |
| subjects affected / exposed                           | 18 / 436 (4.13%)  | 32 / 464 (6.90%)            |  |
| occurrences (all)                                     | 21                | 35                          |  |
| Infections and infestations                           |                   |                             |  |
| Upper Respiratory Tract Infection                     |                   |                             |  |
| subjects affected / exposed                           | 53 / 436 (12.16%) | 60 / 464 (12.93%)           |  |
| occurrences (all)                                     | 69                | 72                          |  |
| Nasopharyngitis                                       |                   |                             |  |
| subjects affected / exposed                           | 24 / 436 (5.50%)  | 21 / 464 (4.53%)            |  |
| occurrences (all)                                     | 28                | 31                          |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date              | Amendment   |
|-------------------|---|
| 17 September 2008 | Following the FDA comments that stopping the trial for futility could reduce the chance of having interpretable results (especially if the benefit is lower than the 30% assumption of the protocol) or the possibility to have meaningful information in the label, it had been decided to remove the futility stopping boundaries for the 3 planned interim analyses of the protocol. This decision was endorsed by the Data Monitoring Committee of the study prior to performing the first interim analysis. Since the efficacy and futility boundaries were computed considering both boundaries simultaneously, the removal of the futility boundary resulted in minor changes to the previously proposed efficacy boundary. Consequently, the EFC5314/CLARINET protocol was amended to remove the futility stopping boundaries and to make subsequent changes to the efficacy stopping boundaries, final significance level, and required number of primary events. The required number of primary events needed for this event driven trial decreased slightly from 174 to 172, and the final significance level changed from 0.037 to 0.035. |

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/23782178>