



## Clinical trial results:

### A Phase III, Double-Blind, Randomized, Placebo-Controlled, Multicenter Clinical Trial to Study the Safety, Tolerability, Efficacy, and Immunogenicity of V212 in Recipients of Autologous Hematopoietic Cell Transplants (HCTs)

#### Summary

|                          |                               |
|--------------------------|-------------------------------|
| EudraCT number           | 2010-020150-34                |
| Trial protocol           | DE NL ES SE CZ GB LT IT BE PT |
| Global end of trial date | 23 December 2015              |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 04 December 2016 |
| First version publication date | 04 December 2016 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | V212-001 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01229267 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Merck Sharp & Dohme Corp.  |
| Sponsor organisation address | 2000 Galloping Hill Road, Kenilworth, NJ, United States, 07033                               |
| Public contact               | Clinical Trials Disclosure, Merck Sharp & Dohme Corp.,<br>ClinicalTrialsDisclosure@merck.com |
| Scientific contact           | Clinical Trials Disclosure, Merck Sharp & Dohme Corp.,<br>ClinicalTrialsDisclosure@merck.com |

Notes:

#### Paediatric regulatory details

|  |    |
|--|----|
| Is trial part of an agreed paediatric investigation plan (PIP)       | No |
| 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? | No |

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 23 December 2015 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 23 December 2015 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 23 December 2015 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

This is a study to determine whether investigational V212 reduces the incidence of herpes zoster (HZ) compared to placebo when administered to recipients of autologous hematopoietic cell transplants (auto-HCT).

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 30 November 2010 |
| Long term follow-up planned                               | No               |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Argentina: 16          |
| Country: Number of subjects enrolled | Australia: 7           |
| Country: Number of subjects enrolled | Belgium: 70            |
| Country: Number of subjects enrolled | Brazil: 25             |
| Country: Number of subjects enrolled | Canada: 21             |
| Country: Number of subjects enrolled | Colombia: 34           |
| Country: Number of subjects enrolled | Croatia: 10            |
| Country: Number of subjects enrolled | Czech Republic: 66     |
| Country: Number of subjects enrolled | Ecuador: 3             |
| Country: Number of subjects enrolled | France: 23             |
| Country: Number of subjects enrolled | Germany: 100           |
| Country: Number of subjects enrolled | Israel: 44             |
| Country: Number of subjects enrolled | Italy: 38              |
| Country: Number of subjects enrolled | Korea, Republic of: 61 |
| Country: Number of subjects enrolled | Lithuania: 20          |
| Country: Number of subjects enrolled | Mexico: 12             |
| Country: Number of subjects enrolled | Netherlands: 6         |
| Country: Number of subjects enrolled | Panama: 10             |
| Country: Number of subjects enrolled | Peru: 12               |

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Portugal: 14           |
| Country: Number of subjects enrolled | Puerto Rico: 2         |
| Country: Number of subjects enrolled | Russian Federation: 14 |
| Country: Number of subjects enrolled | Spain: 42              |
| Country: Number of subjects enrolled | Sweden: 16             |
| Country: Number of subjects enrolled | United Kingdom: 24     |
| Country: Number of subjects enrolled | United States: 540     |
| Worldwide total number of subjects   | 1230                   |
| EEA total number of subjects         | 429                    |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 982 |
| From 65 to 84 years                       | 248 |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

This study enrolled men and women 18 years of age or older who were varicella history positive (or VZV antibody positive) and were scheduled to receive an auto-HCT for treatment of lymphoma or other indication (including any other malignancies) within 60 days of enrollment. Additional inclusion and exclusion criteria applied.

### Pre-assignment

Screening details:

A total of 1323 participants were screened and 1257 were randomized. Twenty-seven participants were removed from all analyses due to the identification of major Good Clinical Practice compliance issues at a single site. Thus, a total of 1230 participants were enrolled in the study.

### 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          |

### Arms

|                              |  |
|------------------------------|--|
| Are arms mutually exclusive? | Yes  |
| <b>Arm title</b>             | V212 Consistency Lots (excluding High Antigen Lot) |

Arm description:

V212 consistency Lot 1, 2, or 3 (Excluding High Antigen Lot) administered by subcutaneous injection 30 days before and 30, 60, and 90 days after auto-HCT.

|  |   |
|--|---|
| Arm type                               | Experimental  |
| Investigational medicinal product name | V212  |
| Investigational medicinal product code |   |
| Other name                             | Inactivated Varicella-Zoster (VZV) vaccine Consistency Lot 1, 2, or 3 |
| Pharmaceutical forms                   | Powder and solution for solution for injection                        |
| Routes of administration               | Subcutaneous use  |

Dosage and administration details:

0.5-mL subcutaneous injection alternating deltoid muscles for consecutive vaccinations

|                  |                       |
|------------------|-----------------------|
| <b>Arm title</b> | V212 High Antigen Lot |
|------------------|-----------------------|

Arm description:

V212 High Antigen Lot administered by subcutaneous injection 30 days before and 30, 60, and 90 days after auto-HCT.

|  |   |
|--|---|
| Arm type                               | Experimental  |
| Investigational medicinal product name | V212  |
| Investigational medicinal product code |   |
| Other name                             | Inactivated Varicella-Zoster (VZV) vaccine High Antigen Lot |
| Pharmaceutical forms                   | Powder and solution for solution for injection              |
| Routes of administration               | Subcutaneous use  |

Dosage and administration details:

0.5-mL subcutaneous injection alternating deltoid muscles for consecutive vaccinations

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

Arm description:

Placebo to V212 administered by subcutaneous injection 30 days before and 30, 60, and 90 days after auto-HCT.

|          |         |
|----------|---------|
| Arm type | Placebo |
|----------|---------|

|  |  |
|--|--|
| Investigational medicinal product name | Placebo  |
| Investigational medicinal product code |  |
| Other name                             | Placebo to V212                                |
| Pharmaceutical forms                   | Powder and solution for solution for injection |
| Routes of administration               | Subcutaneous use                               |

Dosage and administration details:

0.5-mL subcutaneous injection alternating deltoid muscles for consecutive vaccinations

| <b>Number of subjects in period 1</b> | V212 Consistency Lots (excluding High Antigen Lot) | V212 High Antigen Lot | Placebo |
|---------------------------------------|--|-----------------------|---------|
| Started                               | 560  | 106                   | 564     |
| Received Vaccination 1                | 554  | 104                   | 556     |
| Received Vaccination 2                | 502  | 94                    | 511     |
| Received Vaccination 3                | 478  | 89                    | 491     |
| Received Vaccination 4                | 453  | 87                    | 477     |
| Completed                             | 311  | 71                    | 344     |
| Not completed                         | 249  | 35                    | 220     |
| Consent withdrawn by subject          | 77   | 14                    | 59      |
| Physician decision                    | 27   | 3                     | 25      |
| Adverse event, non-fatal              | 13   | 2                     | 10      |
| Death                                 | 112  | 13                    | 103     |
| Lost to follow-up                     | 19   | 3                     | 22      |
| Progressive disease                   | -  | -                     | 1       |
| Protocol deviation                    | 1  | -                     | -       |

## Baseline characteristics

### Reporting groups

|  |  |
|--|--|
| Reporting group title  | V212 Consistency Lots (excluding High Antigen Lot) |
| Reporting group description:<br>V212 consistency Lot 1, 2, or 3 (Excluding High Antigen Lot) administered by subcutaneous injection 30 days before and 30, 60, and 90 days after auto-HCT. |  |
| Reporting group title  | V212 High Antigen Lot                              |
| Reporting group description:<br>V212 High Antigen Lot administered by subcutaneous injection 30 days before and 30, 60, and 90 days after auto-HCT.  |  |
| Reporting group title  | Placebo  |
| Reporting group description:<br>Placebo to V212 administered by subcutaneous injection 30 days before and 30, 60, and 90 days after auto-HCT.  |  |

| Reporting group values                | V212 Consistency Lots (excluding High Antigen Lot) | V212 High Antigen Lot | Placebo |
|---------------------------------------|--|-----------------------|---------|
| Number of subjects                    | 560  | 106                   | 564     |
| Age Categorical<br>Units: Subjects    |  |                       |         |
| Adults (18-64 years)                  | 448  | 83                    | 451     |
| From 65-84 years                      | 112  | 23                    | 113     |
| Age Continuous<br>Units: years        |  |                       |         |
| arithmetic mean                       | 54.1   | 54.3                  | 54.1    |
| standard deviation                    | ± 12.6   | ± 12.2                | ± 12.2  |
| Gender Categorical<br>Units: Subjects |  |                       |         |
| Female                                | 203  | 48                    | 204     |
| Male                                  | 357  | 58                    | 360     |

| Reporting group values                | Total |  |  |
|---------------------------------------|-------|--|--|
| Number of subjects                    | 1230  |  |  |
| Age Categorical<br>Units: Subjects    |       |  |  |
| Adults (18-64 years)                  | 982   |  |  |
| From 65-84 years                      | 248   |  |  |
| Age Continuous<br>Units: years        |       |  |  |
| arithmetic mean                       | -     |  |  |
| standard deviation                    | -     |  |  |
| Gender Categorical<br>Units: Subjects |       |  |  |
| Female                                | 455   |  |  |
| Male                                  | 775   |  |  |

## End points

### End points reporting groups

|  |  |
|--|--|
| Reporting group title  | V212 Consistency Lots (excluding High Antigen Lot) |
| Reporting group description:<br>V212 consistency Lot 1, 2, or 3 (Excluding High Antigen Lot) administered by subcutaneous injection 30 days before and 30, 60, and 90 days after auto-HCT.         |  |
| Reporting group title  | V212 High Antigen Lot                              |
| Reporting group description:<br>V212 High Antigen Lot administered by subcutaneous injection 30 days before and 30, 60, and 90 days after auto-HCT.  |  |
| Reporting group title  | Placebo  |
| Reporting group description:<br>Placebo to V212 administered by subcutaneous injection 30 days before and 30, 60, and 90 days after auto-HCT.  |  |
| Subject analysis set title   | All V212 (including High Antigen Lot)              |
| Subject analysis set type  | Safety analysis                                    |
| Subject analysis set description:<br>V212 Consistency Lot 1, 2, 3 or High Antigen Lot administered by subcutaneous injection 30 days before and 30, 60, and 90 days after auto-HCT.                |  |
| Subject analysis set title   | Placebo  |
| Subject analysis set type  | Safety analysis                                    |
| Subject analysis set description:<br>Placebo to V212 administered by subcutaneous injection 30 days before and 30, 60, and 90 days after auto-HCT. Follow-up is for up to approximately 57 months. |  |

### Primary: Incidence of Confirmed Herpes-Zoster

|   |   |
|---|---|
| End point title   | Incidence of Confirmed Herpes-Zoster <sup>[1]</sup> |
| End point description:<br>Clinical criteria for suspected HZ cases were the development of a papular or vesicular rash with a dermatomal or generalized distribution, or in the absence of a rash, clinical suspicion of VZV infection with or without the detection of VZV in diagnostic specimens from blood, cerebrospinal fluid, lung, liver, or other organ. All suspected cases of HZ were subjected to adjudication by the Clinical Adjudication Committee (CAC). Case confirmation was based on skin lesion polymerase chain reaction, if available, or by adjudication of the clinical case description by the CAC, conducted according to the CAC Standard Operations Procedure. This analysis was based on Modified Intent-to-Treat (MITT) population. The MITT population included all randomized participants who received at least one dose of vaccination and underwent auto-HCT. This endpoint did not apply to participants receiving the V212 High Antigen Lot. |   |
| End point type  | Primary   |
| End point timeframe:<br>Up to approximately 57 months   |   |

#### Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint did not apply to participants receiving the V212 High Antigen lot.

| End point values                             | V212 Consistency Lots (excluding High Antigen Lot) | Placebo         |  |  |
|--|--|-----------------|--|--|
| Subject group type                           | Reporting group                                    | Reporting group |  |  |
| Number of subjects analysed                  | 538  | 535             |  |  |
| Units: Number of cases per 1000 person years |  |                 |  |  |
| number (confidence interval 95%)             | 32.889   | 91.883          |  |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Vaccine Efficacy: Incidence of Confirmed HZ                  |
| Statistical analysis description:   |  |
| Vaccine efficacy was calculated as 1 minus the hazard ratio of HZ in the V212 (excluding High Antigen Lot) group versus the placebo group. The success criterion for vaccine efficacy required that the lower bound of the 95% CI is >0.25. |  |
| Comparison groups   | Placebo v V212 Consistency Lots (excluding High Antigen Lot) |
| Number of subjects included in analysis   | 1073   |
| Analysis specification  | Pre-specified  |
| Analysis type   | other <sup>[2]</sup>   |
| Parameter estimate  | Vaccine Efficacy   |
| Point estimate  | 0.638  |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | 0.484  |
| upper limit   | 0.746  |

Notes:

[2] - Point estimate and 95% Confidence Interval (CI) of vaccine efficacy were obtained from a Cox proportional hazards regression model, adjusting for age (< 50 years of age versus ≥ 50 years of age), and expected duration of antiviral prophylaxis (≤ 3 months versus 3 to 6 months after auto-HCT).

## Primary: Percentage of Participants with One or More Serious Adverse Event

|  |   |
|--|---|
| End point title  | Percentage of Participants with One or More Serious Adverse Event |
| End point description:   |   |
| An adverse event (AE) is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the sponsor's product, whether or not considered related to the use of the product. A serious adverse event (SAE) is an AE that results in death, is life threatening, results in a persistent or significant disability or incapacity, results in or prolongs an existing hospitalization, is a congenital anomaly or birth defect, is a cancer, is an overdose, or is another important medical event. The analysis population included all participants who received ≥ 1 dose of vaccination or placebo and had safety follow-up. One participant randomized to placebo was cross-treated; this participant was excluded from the safety analyses. Safety analyses in the study were based on the pooled data from Consistency Lot 1, 2, 3 and High Antigen Lot. |   |
| End point type   | Primary   |
| End point timeframe:   |   |
| Up to 28 days after vaccination 4  |   |

| End point values                  | All V212<br>(including High Antigen Lot) | Placebo              |  |  |
|-----------------------------------|--|----------------------|--|--|
| Subject group type                | Subject analysis set                     | Subject analysis set |  |  |
| Number of subjects analysed       | 657                                      | 554                  |  |  |
| Units: Percentage of participants |  |                      |  |  |
| number (not applicable)           | 32.9                                     | 32.7                 |  |  |



## Statistical analyses

|   |   |
|---|---|
| <b>Statistical analysis title</b>   | Risk Difference                                 |
| Statistical analysis description:   |   |
| Risk difference and 95% confidence intervals are based on Miettinen & Nurminen method stratified by age and intended duration of antiviral prophylaxis. |   |
| Comparison groups   | All V212 (including High Antigen Lot) v Placebo |
| Number of subjects included in analysis   | 1211  |
| Analysis specification  | Pre-specified                                   |
| Analysis type   | other   |
| Parameter estimate  | Risk difference (RD)                            |
| Point estimate  | 0.2   |
| Confidence interval   |   |
| level   | 95 %  |
| sides   | 2-sided   |
| lower limit   | -5.1  |
| upper limit   | 5.5   |

## Secondary: Incidence of Moderate to Severe Herpes-Zoster-Associated Pain

|   |  |
|---|--|
| End point title   | Incidence of Moderate to Severe Herpes-Zoster-Associated |
| End point description:  |  |
| Moderate to severe HZ-associated pain was defined as 2 or more occurrences of a score 3 or greater (0-to-10 scale, where 0 is no pain and 10 is pain as bad as you can imagine) on the Zoster Brief Pain Inventory at any time from HZ onset through the end of the 6 month HZ-follow-up period. This analysis was based on Modified Intent-to-Treat (MITT) population. The MITT population included all randomized participants who received at least one dose of vaccination and underwent auto-HCT. This endpoint did not apply to participants receiving the V212 High Antigen Lot. |  |
| End point type  | Secondary  |
| End point timeframe:  |  |
| Up to 6 months after the onset of HZ  |  |

### Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint did not apply to participants receiving the V212 High Antigen lot.

| End point values                             | V212 Consistency Lots (excluding High Antigen Lot) | Placebo           |  |  |
|--|--|-------------------|--|--|
| Subject group type                           | Reporting group                                    | Reporting group   |  |  |
| Number of subjects analysed                  | 538  | 535               |  |  |
| Units: Number of cases per 1000 person years |  |                   |  |  |
| number (confidence interval 95%)             | 14.878 (8.958 to 23.234)                           | 49.601 (37.941 to |  |  |

## Statistical analyses

|   |  |
|---|--|
| <b>Statistical analysis title</b>   | Vaccine Efficacy: Incidence of HZ-associated Pain            |
| Statistical analysis description:   |  |
| Vaccine efficacy was calculated as 1 minus the hazard ratio of HZ pain in the V212 (excluding High Antigen Lot) group versus the placebo group. |  |
| Comparison groups   | Placebo v V212 Consistency Lots (excluding High Antigen Lot) |
| Number of subjects included in analysis   | 1073   |
| Analysis specification  | Pre-specified  |
| Analysis type   | other <sup>[4]</sup>   |
| Parameter estimate  | Vaccine efficacy   |
| Point estimate  | 0.695  |
| Confidence interval   |  |
| level   | 95 %   |
| sides   | 2-sided  |
| lower limit   | 0.49   |
| upper limit   | 0.818  |

Notes:

[4] - Point estimate and 95% CI of vaccine efficacy were obtained from a Cox proportional hazards regression model, adjusting for vaccination group, age (<50 years of age versus ≥50 years of age), and expected duration of antiviral prophylaxis (≤3 months versus >3 and ≤6 months after auto-HCT).

## Secondary: Incidence of Herpes-Zoster Complications

|   |   |
|---|---|
| <b>End point title</b>  | Incidence of Herpes-Zoster Complications <sup>[5]</sup> |
| End point description:  |   |
| The composite efficacy endpoint of the incidence of HZ complications was defined as the occurrence of any of the following during the study: hospitalization or prolongation of hospitalization due to HZ, disseminated HZ (including disseminated HZ rash or VZV viremia), visceral HZ, ophthalmic HZ, neurological impairment due to HZ, or administration of intravenous acyclovir therapy for treatment of HZ. This analysis was based on Modified Intent-to-Treat (MITT) population. The MITT population included all randomized participants who received at least one dose of vaccination and underwent auto-HCT. This endpoint did not apply to participants receiving the V212 High Antigen Lot. |   |
| <b>End point type</b>   | Secondary   |
| End point timeframe:  |   |
| Up to approximately 57 months   |   |

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint did not apply to participants receiving the V212 High Antigen lot.

| <b>End point values</b>                      | V212 Consistency Lots (excluding High Antigen Lot) | Placebo         |  |  |
|--|--|-----------------|--|--|
| Subject group type                           | Reporting group                                    | Reporting group |  |  |
| Number of subjects analysed                  | 538  | 535             |  |  |
| Units: Number of cases per 1000 person years |  |                 |  |  |
| number (confidence interval 95%)             | 9.397 (4.855)                                      | 35.77 (25.996)  |  |  |

## Statistical analyses

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | Vaccine Efficacy: Incidence of HZ Complications              |
| Statistical analysis description:  |  |
| Vaccine efficacy was calculated as 1 minus the hazard ratio of HZ complications in the V212 [excluding High Antigen Lot] group versus the placebo group. |  |
| Comparison groups  | Placebo v V212 Consistency Lots (excluding High Antigen Lot) |
| Number of subjects included in analysis  | 1073   |
| Analysis specification   | Pre-specified  |
| Analysis type  | other <sup>[6]</sup>   |
| Parameter estimate   | Vaccine efficacy   |
| Point estimate   | 0.735  |
| Confidence interval  |  |
| level  | 95 %   |
| sides  | 2-sided  |
| lower limit  | 0.498  |
| upper limit  | 0.86   |

Notes:

[6] - Point estimate and 95% CI of vaccine efficacy were obtained from a Cox proportional hazards regression model, adjusting for vaccination group, age (<50 years of age versus ≥50 years of age), and expected duration of antiviral prophylaxis (≤3 months versus >3 and ≤6 months after auto-HCT).

## Secondary: Incidence of Postherpetic Neuralgia

|  |  |
|--|--|
| End point title  | Incidence of Postherpetic Neuralgia <sup>[7]</sup> |
| End point description:   |  |
| Postherpetic Neuralgia (PHN) was defined as pain in the area of the HZ rash with a pain in the last 24 hours score of 3 or greater (on a 0 to 10 scale, where 0 is no pain and 10 is pain as bad as you can imagine) on the ZBPI that persists or appears greater than or equal to 90 days after HZ rash onset. This analysis was based on Modified Intent-to-Treat (MITT) population. The MITT population included all randomized participants who received at least one dose of vaccination and underwent auto-HCT. This endpoint did not apply to participants receiving the V212 High Antigen Lot. |  |
| End point type   | Secondary  |

End point timeframe:

Up to 6 months after the onset of HZ rash

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: This endpoint did not apply to participants receiving the V212 High Antigen lot.

| End point values                             | V212 Consistency Lots (excluding High Antigen Lot) | Placebo                  |  |  |
|--|--|--------------------------|--|--|
| Subject group type                           | Reporting group                                    | Reporting group          |  |  |
| Number of subjects analysed                  | 538  | 535                      |  |  |
| Units: Number of cases per 1000 person years |  |                          |  |  |
| number (confidence interval 95%)             | 2.349 (0.484 to 6.865)                             | 14.636 (8.674 to 23.132) |  |  |

## Statistical analyses

|  |  |
|--|--|
| <b>Statistical analysis title</b>  | Vaccine Efficacy: Incidence of PHN                           |
| Statistical analysis description:<br>Vaccine efficacy was calculated as 1 minus the hazard ratio of PHN in the V212 [excluding High Antigen Lot] group versus placebo group. |  |
| Comparison groups  | Placebo v V212 Consistency Lots (excluding High Antigen Lot) |
| Number of subjects included in analysis  | 1073   |
| Analysis specification   | Pre-specified  |
| Analysis type  | other <sup>[8]</sup>   |
| Parameter estimate   | Vaccine efficacy   |
| Point estimate   | 0.837  |
| Confidence interval  |  |
| level  | 95 %   |
| sides  | 2-sided  |
| lower limit  | 0.446  |
| upper limit  | 0.952  |

Notes:

[8] - Point estimate and 95% CI of vaccine efficacy were obtained from a Cox proportional hazards regression model, adjusting for age (<50 years of age versus ≥50 years of age), and expected duration of antiviral prophylaxis (≤3 months versus 3 to 6 months after auto-HCT).

## Other pre-specified: Percentage of Participants with Study Medication Withdrawn due to an Adverse Event

|  |  |
|--|--|
| End point title  | Percentage of Participants with Study Medication Withdrawn due to an Adverse Event |
| End point description:<br>An AE is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the sponsor's product, whether or not considered related to the use of the product. The analysis population included all subjects who received ≥1 dose of vaccination or placebo and had safety follow-up. One participant randomized to placebo was cross-treated; this participant was excluded from the safety analyses. Safety analyses in the study were based on the pooled data from Consistency Lot 1, 2, 3 and High Antigen Lot. |  |
| End point type   | Other pre-specified  |
| End point timeframe:<br>Up to 28 days after vaccination 4  |  |

| End point values                  | All V212<br>(including High Antigen Lot) | Placebo              |  |  |
|-----------------------------------|--|----------------------|--|--|
| Subject group type                | Subject analysis set                     | Subject analysis set |  |  |
| Number of subjects analysed       | 657                                      | 554                  |  |  |
| Units: Percentage of participants |  |                      |  |  |
| number (not applicable)           | 3  | 3.1                  |  |  |

## **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Up to approximately 57 months after vaccination 1

Adverse event reporting additional description:

All Subjects as Treated population included all who received  $\geq 1$  dose of vaccination or placebo and had safety follow-up. One participant randomized to placebo was cross-treated; this participant was excluded from the safety analyses. Safety analyses in the study were based on the pooled data from Consistency Lot 1, 2, 3 and High Antigen Lot.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 19.0 |
|--------------------|------|

### Reporting groups

|                       |                                   |
|-----------------------|-----------------------------------|
| Reporting group title | V212 [including High Antigen Lot] |
|-----------------------|-----------------------------------|

Reporting group description:

V212 Consistency Lot 1, 2, 3 or High Antigen Lot administered by subcutaneous injection 30 days before and 30, 60, and 90 days after auto-HCT.

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

Reporting group description:

Placebo to V212 administered by subcutaneous injection 30 days before and 30, 60, and 90 days after auto-HCT.

| Serious adverse events  | V212 [including High Antigen Lot] | Placebo            |  |
|---|-----------------------------------|--------------------|--|
| Total subjects affected by serious adverse events                   |                                   |                    |  |
| subjects affected / exposed   | 420 / 657 (63.93%)                | 374 / 554 (67.51%) |  |
| number of deaths (all causes)                                       | 136                               | 107                |  |
| number of deaths resulting from adverse events                      | 0                                 | 0                  |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                                   |                    |  |
| Acute leukaemia   |                                   |                    |  |
| subjects affected / exposed   | 1 / 657 (0.15%)                   | 1 / 554 (0.18%)    |  |
| occurrences causally related to treatment / all                     | 0 / 1                             | 0 / 1              |  |
| deaths causally related to treatment / all                          | 0 / 1                             | 0 / 1              |  |
| Acute myeloid leukaemia   |                                   |                    |  |
| subjects affected / exposed   | 2 / 657 (0.30%)                   | 2 / 554 (0.36%)    |  |
| occurrences causally related to treatment / all                     | 0 / 2                             | 0 / 2              |  |
| deaths causally related to treatment / all                          | 0 / 0                             | 0 / 0              |  |
| Acute myeloid leukaemia recurrent                                   |                                   |                    |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                                     | 0 / 657 (0.00%) | 3 / 554 (0.54%) |  |
| occurrences causally related to treatment / all                 | 0 / 0           | 0 / 4           |  |
| deaths causally related to treatment / all                      | 0 / 0           | 0 / 2           |  |
| Acute promyelocytic leukaemia                                   |                 |                 |  |
| subjects affected / exposed                                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all                 | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                      | 0 / 0           | 0 / 1           |  |
| Adenocarcinoma gastric  |                 |                 |  |
| subjects affected / exposed                                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all                 | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                      | 0 / 0           | 0 / 1           |  |
| Anaplastic large cell lymphoma T- and null-cell types           |                 |                 |  |
| subjects affected / exposed                                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all                 | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                      | 0 / 1           | 0 / 0           |  |
| Anaplastic large cell lymphoma T- and null-cell types recurrent |                 |                 |  |
| subjects affected / exposed                                     | 0 / 657 (0.00%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all                 | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all                      | 0 / 0           | 0 / 1           |  |
| Anaplastic large-cell lymphoma                                  |                 |                 |  |
| subjects affected / exposed                                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all                 | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                      | 0 / 1           | 0 / 0           |  |
| Angiocentric lymphoma   |                 |                 |  |
| subjects affected / exposed                                     | 0 / 657 (0.00%) | 3 / 554 (0.54%) |  |
| occurrences causally related to treatment / all                 | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all                      | 0 / 0           | 0 / 0           |  |
| Angioimmunoblastic T-cell lymphoma recurrent                    |                 |                 |  |
| subjects affected / exposed                                     | 1 / 657 (0.15%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all                 | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all                      | 0 / 1           | 0 / 1           |  |
| B-cell lymphoma   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 657 (0.00%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| B-cell lymphoma recurrent                       |                 |                 |  |
| subjects affected / exposed                     | 3 / 657 (0.46%) | 5 / 554 (0.90%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| B-cell lymphoma stage IV                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Basal cell carcinoma                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 3 / 554 (0.54%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Basosquamous carcinoma                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bladder cancer                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bladder cancer recurrent                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Breast cancer                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Breast cancer recurrent                         |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Central nervous system lymphoma                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Cholangiocarcinoma                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic lymphocytic leukaemia recurrent         |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Chronic myeloid leukaemia                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colon adenoma                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colon cancer metastatic                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colorectal cancer                               |                 |                 |  |
| subjects affected / exposed                     | 2 / 657 (0.30%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diffuse large B-cell lymphoma                   |                 |                 |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                                     | 10 / 657 (1.52%) | 10 / 554 (1.81%) |  |
| occurrences causally related to treatment / all                 | 0 / 11           | 0 / 11           |  |
| deaths causally related to treatment / all                      | 0 / 5            | 0 / 5            |  |
| Diffuse large B-cell lymphoma recurrent                         |                  |                  |  |
| subjects affected / exposed                                     | 14 / 657 (2.13%) | 10 / 554 (1.81%) |  |
| occurrences causally related to treatment / all                 | 0 / 14           | 0 / 10           |  |
| deaths causally related to treatment / all                      | 0 / 6            | 0 / 6            |  |
| Diffuse large B-cell lymphoma refractory                        |                  |                  |  |
| subjects affected / exposed                                     | 1 / 657 (0.15%)  | 0 / 554 (0.00%)  |  |
| occurrences causally related to treatment / all                 | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all                      | 0 / 1            | 0 / 0            |  |
| Extranodal marginal zone B-cell lymphoma (MALT type) recurrent  |                  |                  |  |
| subjects affected / exposed                                     | 1 / 657 (0.15%)  | 0 / 554 (0.00%)  |  |
| occurrences causally related to treatment / all                 | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all                      | 0 / 0            | 0 / 0            |  |
| Follicle centre lymphoma, follicular grade I, II, III recurrent |                  |                  |  |
| subjects affected / exposed                                     | 0 / 657 (0.00%)  | 1 / 554 (0.18%)  |  |
| occurrences causally related to treatment / all                 | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all                      | 0 / 0            | 0 / 0            |  |
| Hodgkin's disease   |                  |                  |  |
| subjects affected / exposed                                     | 8 / 657 (1.22%)  | 5 / 554 (0.90%)  |  |
| occurrences causally related to treatment / all                 | 0 / 8            | 0 / 7            |  |
| deaths causally related to treatment / all                      | 0 / 2            | 0 / 1            |  |
| Hodgkin's disease nodular sclerosis                             |                  |                  |  |
| subjects affected / exposed                                     | 1 / 657 (0.15%)  | 0 / 554 (0.00%)  |  |
| occurrences causally related to treatment / all                 | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all                      | 0 / 0            | 0 / 0            |  |
| Hodgkin's disease recurrent                                     |                  |                  |  |
| subjects affected / exposed                                     | 7 / 657 (1.07%)  | 6 / 554 (1.08%)  |  |
| occurrences causally related to treatment / all                 | 0 / 8            | 0 / 6            |  |
| deaths causally related to treatment / all                      | 0 / 3            | 0 / 1            |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| Langerhans' cell histiocytosis<br>subjects affected / exposed              | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to<br>treatment / all                         | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                              | 0 / 0           | 0 / 0           |  |
| Laryngeal squamous cell carcinoma<br>subjects affected / exposed           | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to<br>treatment / all                         | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                              | 0 / 0           | 0 / 0           |  |
| Leukaemia recurrent<br>subjects affected / exposed                         | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to<br>treatment / all                         | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                              | 0 / 0           | 0 / 1           |  |
| Lung neoplasm malignant<br>subjects affected / exposed                     | 1 / 657 (0.15%) | 2 / 554 (0.36%) |  |
| occurrences causally related to<br>treatment / all                         | 0 / 1           | 0 / 2           |  |
| deaths causally related to<br>treatment / all                              | 0 / 1           | 0 / 0           |  |
| Lymphoma<br>subjects affected / exposed                                    | 9 / 657 (1.37%) | 6 / 554 (1.08%) |  |
| occurrences causally related to<br>treatment / all                         | 0 / 9           | 0 / 7           |  |
| deaths causally related to<br>treatment / all                              | 0 / 2           | 0 / 0           |  |
| Lymphoplasmacytoid<br>lymphoma/immunocytoma<br>subjects affected / exposed | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to<br>treatment / all                         | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                              | 0 / 0           | 0 / 0           |  |
| Malignant lymphoid neoplasm<br>subjects affected / exposed                 | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to<br>treatment / all                         | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                              | 0 / 0           | 0 / 1           |  |
| Malignant melanoma<br>subjects affected / exposed                          | 1 / 657 (0.15%) | 4 / 554 (0.72%) |  |
| occurrences causally related to<br>treatment / all                         | 0 / 1           | 0 / 4           |  |
| deaths causally related to<br>treatment / all                              | 0 / 0           | 0 / 0           |  |
| Mantle cell lymphoma   |                 |                 |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 657 (0.15%)  | 4 / 554 (0.72%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 2            |  |
| Mantle cell lymphoma recurrent                  |                  |                  |  |
| subjects affected / exposed                     | 10 / 657 (1.52%) | 9 / 554 (1.62%)  |  |
| occurrences causally related to treatment / all | 0 / 10           | 0 / 9            |  |
| deaths causally related to treatment / all      | 0 / 4            | 0 / 2            |  |
| Metastases to meninges                          |                  |                  |  |
| subjects affected / exposed                     | 1 / 657 (0.15%)  | 0 / 554 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Myelodysplastic syndrome                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 657 (0.15%)  | 0 / 554 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Neuroendocrine carcinoma                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 657 (0.15%)  | 0 / 554 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Non-Hodgkin's lymphoma                          |                  |                  |  |
| subjects affected / exposed                     | 6 / 657 (0.91%)  | 3 / 554 (0.54%)  |  |
| occurrences causally related to treatment / all | 0 / 6            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 1            |  |
| Non-Hodgkin's lymphoma recurrent                |                  |                  |  |
| subjects affected / exposed                     | 10 / 657 (1.52%) | 13 / 554 (2.35%) |  |
| occurrences causally related to treatment / all | 0 / 11           | 0 / 13           |  |
| deaths causally related to treatment / all      | 0 / 5            | 0 / 7            |  |
| Non-Hodgkin's lymphoma refractory               |                  |                  |  |
| subjects affected / exposed                     | 1 / 657 (0.15%)  | 0 / 554 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Nonkeratinising carcinoma of nasopharynx        |                  |                  |  |

|  |                   |                  |  |
|--|-------------------|------------------|--|
| subjects affected / exposed                      | 1 / 657 (0.15%)   | 0 / 554 (0.00%)  |  |
| occurrences causally related to treatment / all  | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all       | 0 / 0             | 0 / 0            |  |
| Pancreatic carcinoma                             |                   |                  |  |
| subjects affected / exposed                      | 1 / 657 (0.15%)   | 0 / 554 (0.00%)  |  |
| occurrences causally related to treatment / all  | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all       | 0 / 1             | 0 / 0            |  |
| Papillary thyroid cancer                         |                   |                  |  |
| subjects affected / exposed                      | 1 / 657 (0.15%)   | 3 / 554 (0.54%)  |  |
| occurrences causally related to treatment / all  | 0 / 1             | 0 / 3            |  |
| deaths causally related to treatment / all       | 0 / 0             | 0 / 0            |  |
| Paraneoplastic syndrome                          |                   |                  |  |
| subjects affected / exposed                      | 2 / 657 (0.30%)   | 0 / 554 (0.00%)  |  |
| occurrences causally related to treatment / all  | 0 / 2             | 0 / 0            |  |
| deaths causally related to treatment / all       | 0 / 0             | 0 / 0            |  |
| Pericardial effusion malignant                   |                   |                  |  |
| subjects affected / exposed                      | 1 / 657 (0.15%)   | 0 / 554 (0.00%)  |  |
| occurrences causally related to treatment / all  | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all       | 0 / 0             | 0 / 0            |  |
| Peripheral T-cell lymphoma unspecified           |                   |                  |  |
| subjects affected / exposed                      | 3 / 657 (0.46%)   | 2 / 554 (0.36%)  |  |
| occurrences causally related to treatment / all  | 0 / 3             | 0 / 2            |  |
| deaths causally related to treatment / all       | 0 / 2             | 0 / 2            |  |
| Peripheral T-cell lymphoma unspecified recurrent |                   |                  |  |
| subjects affected / exposed                      | 4 / 657 (0.61%)   | 2 / 554 (0.36%)  |  |
| occurrences causally related to treatment / all  | 0 / 4             | 0 / 2            |  |
| deaths causally related to treatment / all       | 0 / 0             | 0 / 2            |  |
| Plasma cell myeloma                              |                   |                  |  |
| subjects affected / exposed                      | 67 / 657 (10.20%) | 51 / 554 (9.21%) |  |
| occurrences causally related to treatment / all  | 0 / 75            | 0 / 57           |  |
| deaths causally related to treatment / all       | 0 / 24            | 0 / 15           |  |
| Plasma cell myeloma recurrent                    |                   |                  |  |

|  |                  |                  |  |
|--|------------------|------------------|--|
| subjects affected / exposed                            | 50 / 657 (7.61%) | 53 / 554 (9.57%) |  |
| occurrences causally related to treatment / all        | 0 / 51           | 0 / 56           |  |
| deaths causally related to treatment / all             | 0 / 13           | 0 / 15           |  |
| Plasmablastic lymphoma                                 |                  |                  |  |
| subjects affected / exposed                            | 1 / 657 (0.15%)  | 0 / 554 (0.00%)  |  |
| occurrences causally related to treatment / all        | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all             | 0 / 1            | 0 / 0            |  |
| Plasmacytoma   |                  |                  |  |
| subjects affected / exposed                            | 0 / 657 (0.00%)  | 1 / 554 (0.18%)  |  |
| occurrences causally related to treatment / all        | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all             | 0 / 0            | 0 / 0            |  |
| Precursor T-lymphoblastic lymphoma/leukaemia           |                  |                  |  |
| subjects affected / exposed                            | 1 / 657 (0.15%)  | 1 / 554 (0.18%)  |  |
| occurrences causally related to treatment / all        | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all             | 0 / 1            | 0 / 1            |  |
| Precursor T-lymphoblastic lymphoma/leukaemia recurrent |                  |                  |  |
| subjects affected / exposed                            | 1 / 657 (0.15%)  | 0 / 554 (0.00%)  |  |
| occurrences causally related to treatment / all        | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all             | 0 / 1            | 0 / 0            |  |
| Primary mediastinal large B-cell lymphoma              |                  |                  |  |
| subjects affected / exposed                            | 0 / 657 (0.00%)  | 1 / 554 (0.18%)  |  |
| occurrences causally related to treatment / all        | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all             | 0 / 0            | 0 / 1            |  |
| Prostate cancer  |                  |                  |  |
| subjects affected / exposed                            | 1 / 657 (0.15%)  | 1 / 554 (0.18%)  |  |
| occurrences causally related to treatment / all        | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all             | 0 / 0            | 0 / 1            |  |
| Rectal cancer  |                  |                  |  |
| subjects affected / exposed                            | 1 / 657 (0.15%)  | 0 / 554 (0.00%)  |  |
| occurrences causally related to treatment / all        | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all             | 0 / 1            | 0 / 0            |  |
| Rectal cancer recurrent                                |                  |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal cell carcinoma                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Small cell carcinoma                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Squamous cell carcinoma                         |                 |                 |  |
| subjects affected / exposed                     | 2 / 657 (0.30%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Squamous cell carcinoma of skin                 |                 |                 |  |
| subjects affected / exposed                     | 2 / 657 (0.30%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| T-cell lymphoma                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| T-cell lymphoma recurrent                       |                 |                 |  |
| subjects affected / exposed                     | 8 / 657 (1.22%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 8           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 4           | 0 / 0           |  |
| Tumour flare                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular disorders                              |                 |                 |  |
| Aortic aneurysm                                 |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Aortic stenosis                                 |                 |                 |  |
| subjects affected / exposed                     | 2 / 657 (0.30%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Deep vein thrombosis                            |                 |                 |  |
| subjects affected / exposed                     | 7 / 657 (1.07%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 7           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Embolism  |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypertension                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypertensive crisis                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 3 / 554 (0.54%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypotension                                     |                 |                 |  |
| subjects affected / exposed                     | 5 / 657 (0.76%) | 3 / 554 (0.54%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Orthostatic hypotension                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peripheral arterial occlusive disease           |                 |                 |  |



|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                          | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Peripheral artery thrombosis                         |                 |                 |  |
| subjects affected / exposed                          | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Venoocclusive disease                                |                 |                 |  |
| subjects affected / exposed                          | 2 / 657 (0.30%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Venous thrombosis limb                               |                 |                 |  |
| subjects affected / exposed                          | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Pregnancy, puerperium and perinatal conditions       |                 |                 |  |
| Threatened labour                                    |                 |                 |  |
| subjects affected / exposed                          | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| 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 |                 |                 |  |
| Adverse drug reaction                                |                 |                 |  |
| subjects affected / exposed                          | 2 / 657 (0.30%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Asthenia   |                 |                 |  |
| subjects affected / exposed                          | 4 / 657 (0.61%) | 3 / 554 (0.54%) |  |
| occurrences causally related to treatment / all      | 0 / 4           | 0 / 3           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Death  |                 |                 |  |
| subjects affected / exposed                          | 5 / 657 (0.76%) | 4 / 554 (0.72%) |  |
| occurrences causally related to treatment / all      | 0 / 5           | 0 / 4           |  |
| deaths causally related to treatment / all           | 0 / 5           | 0 / 4           |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| Drug withdrawal syndrome                        |                  |                  |  |
| subjects affected / exposed                     | 1 / 657 (0.15%)  | 0 / 554 (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                     | 1 / 657 (0.15%)  | 1 / 554 (0.18%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Influenza like illness                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 657 (0.00%)  | 2 / 554 (0.36%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Malaise   |                  |                  |  |
| subjects affected / exposed                     | 1 / 657 (0.15%)  | 0 / 554 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Mucosal inflammation                            |                  |                  |  |
| subjects affected / exposed                     | 8 / 657 (1.22%)  | 6 / 554 (1.08%)  |  |
| occurrences causally related to treatment / all | 0 / 8            | 1 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Multiple organ dysfunction syndrome             |                  |                  |  |
| subjects affected / exposed                     | 3 / 657 (0.46%)  | 3 / 554 (0.54%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 3            |  |
| Pneumatosis                                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 657 (0.00%)  | 1 / 554 (0.18%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pyrexia   |                  |                  |  |
| subjects affected / exposed                     | 33 / 657 (5.02%) | 26 / 554 (4.69%) |  |
| occurrences causally related to treatment / all | 0 / 37           | 1 / 26           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Systemic inflammatory response syndrome         |                  |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 657 (0.30%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ulcer haemorrhage                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Immune system disorders                         |                 |                 |  |
| Acute graft versus host disease in skin         |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Amyloidosis                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Anaphylactic reaction                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Anaphylactic shock                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Drug hypersensitivity                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Engraftment syndrome                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Graft versus host disease                       |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                         | 0 / 657 (0.00%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all     | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all          | 0 / 0           | 0 / 0           |  |
| Graft versus host disease in gastrointestinal tract |                 |                 |  |
| subjects affected / exposed                         | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all     | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all          | 0 / 0           | 0 / 0           |  |
| Graft versus host disease in liver                  |                 |                 |  |
| subjects affected / exposed                         | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all     | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all          | 0 / 1           | 0 / 0           |  |
| Graft versus host disease in lung                   |                 |                 |  |
| subjects affected / exposed                         | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all     | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all          | 0 / 0           | 0 / 0           |  |
| Graft versus host disease in skin                   |                 |                 |  |
| subjects affected / exposed                         | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all     | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all          | 0 / 0           | 0 / 0           |  |
| Hypersensitivity                                    |                 |                 |  |
| subjects affected / exposed                         | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all     | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all          | 0 / 0           | 0 / 0           |  |
| Primary amyloidosis                                 |                 |                 |  |
| subjects affected / exposed                         | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all     | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all          | 0 / 0           | 0 / 0           |  |
| Reproductive system and breast disorders            |                 |                 |  |
| Acquired phimosis                                   |                 |                 |  |
| subjects affected / exposed                         | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all     | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all          | 0 / 0           | 0 / 0           |  |
| Benign prostatic hyperplasia                        |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 657 (0.15%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Acute pulmonary oedema                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute respiratory failure                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Asthma  |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic obstructive pulmonary disease           |                 |                 |  |
| subjects affected / exposed                     | 3 / 657 (0.46%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dyspnoea  |                 |                 |  |
| subjects affected / exposed                     | 2 / 657 (0.30%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Emphysema                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoxia   |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Idiopathic pneumonia syndrome                   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Interstitial lung disease                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 657 (0.30%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung consolidation                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Lung infiltration                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Obstructive airways disorder                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Organising pneumonia                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oropharyngeal pain                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumomediastinum                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pleural effusion                                |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (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                     | 1 / 657 (0.15%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonitis                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumothorax                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary embolism                              |                 |                 |  |
| subjects affected / exposed                     | 6 / 657 (0.91%) | 5 / 554 (0.90%) |  |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary hypertension                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary mass                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Pulmonary oedema                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Respiratory distress                            |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 3 / 657 (0.46%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Respiratory failure                             |                 |                 |  |
| subjects affected / exposed                     | 3 / 657 (0.46%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| Restrictive pulmonary disease                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sleep apnoea syndrome                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Psychiatric disorders                           |                 |                 |  |
| Anxiety   |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Confusional state                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Delirium  |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Depression                                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 657 (0.30%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Disorientation                                  |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypomania                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mania   |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mental status changes                           |                 |                 |  |
| subjects affected / exposed                     | 2 / 657 (0.30%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Schizoaffective disorder                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Suicide attempt                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |
| Allergic transfusion reaction                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Brain contusion                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Comminuted fracture                             |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Compression fracture                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Delayed engraftment                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Femur fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Foot fracture                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Forearm fracture                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hip fracture                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 3 / 554 (0.54%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infusion related reaction                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Multiple fractures                              |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 657 (0.15%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peroneal nerve injury                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Post lumbar puncture syndrome                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Procedural hypotension                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Seroma  |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal compression fracture                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal fracture                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subdural haematoma                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subdural haemorrhage                            |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Tendon rupture                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Toxicity to various agents                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Transfusion reaction                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Transplant dysfunction                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Traumatic haemothorax                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper limb fracture                             |                 |                 |  |
| subjects affected / exposed                     | 2 / 657 (0.30%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wound dehiscence                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Acute myocardial infarction                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 5 / 657 (0.76%) | 3 / 554 (0.54%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Arrhythmia                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 4 / 657 (0.61%) | 5 / 554 (0.90%) |  |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Atrial flutter                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bradycardia                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac amyloidosis                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 3 / 554 (0.54%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 3           |  |
| Cardiac failure                                 |                 |                 |  |
| subjects affected / exposed                     | 3 / 657 (0.46%) | 4 / 554 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure acute                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure chronic                         |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Cardiac failure congestive                      |                 |                 |  |
| subjects affected / exposed                     | 5 / 657 (0.76%) | 5 / 554 (0.90%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 2           |  |
| Cardiac ventricular thrombosis                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiogenic shock                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Coronary artery disease                         |                 |                 |  |
| subjects affected / exposed                     | 2 / 657 (0.30%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coronary artery occlusion                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myocardial infarction                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pericarditis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Supraventricular tachycardia                    |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 657 (0.15%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tachycardia                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Autonomic nervous system imbalance              |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Carotid artery aneurysm                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Carotid artery disease                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebellar infarction                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebral haemorrhage                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Cerebrovascular accident                        |                 |                 |  |
| subjects affected / exposed                     | 4 / 657 (0.61%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dizziness                                       |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Facial paralysis                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Headache  |                 |                 |  |
| subjects affected / exposed                     | 2 / 657 (0.30%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic encephalopathy                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoglycaemic coma                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intracranial venous sinus thrombosis            |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolic encephalopathy                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Migraine  |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Paraesthesia                                    |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Presyncope                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sciatica  |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Syncope   |                 |                 |  |
| subjects affected / exposed                     | 6 / 657 (0.91%) | 5 / 554 (0.90%) |  |
| occurrences causally related to treatment / all | 0 / 7           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Transient ischaemic attack                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| Abdominal lymphadenopathy                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acquired haemophilia                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Agranulocytosis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Anaemia   |                 |                 |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 3 / 657 (0.46%)  | 3 / 554 (0.54%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Anaemia megaloblastic                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 657 (0.15%)  | 0 / 554 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bone marrow failure                             |                  |                  |  |
| subjects affected / exposed                     | 0 / 657 (0.00%)  | 1 / 554 (0.18%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Febrile neutropenia                             |                  |                  |  |
| subjects affected / exposed                     | 42 / 657 (6.39%) | 38 / 554 (6.86%) |  |
| occurrences causally related to treatment / all | 0 / 44           | 0 / 47           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Heparin-induced thrombocytopenia                |                  |                  |  |
| subjects affected / exposed                     | 0 / 657 (0.00%)  | 1 / 554 (0.18%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Immune thrombocytopenic purpura                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 657 (0.00%)  | 1 / 554 (0.18%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Leukocytosis                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 657 (0.15%)  | 0 / 554 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Lymphadenopathy                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 657 (0.15%)  | 0 / 554 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Methaemoglobinaemia                             |                  |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neutropenia                                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 657 (0.30%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancytopenia                                    |                 |                 |  |
| subjects affected / exposed                     | 4 / 657 (0.61%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all | 1 / 4           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sickle cell anaemia with crisis                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Splenic infarction                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thrombocytopenia                                |                 |                 |  |
| subjects affected / exposed                     | 8 / 657 (1.22%) | 7 / 554 (1.26%) |  |
| occurrences causally related to treatment / all | 0 / 8           | 0 / 7           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ear and labyrinth disorders                     |                 |                 |  |
| Acute vestibular syndrome                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Eye disorders                                   |                 |                 |  |
| Diabetic retinopathy                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intraocular haematoma                           |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Retinal haemorrhage                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vitreous haemorrhage                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| 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                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal pain                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Anal fissure                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Anal incontinence                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Aphthous ulcer                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ascites   |                 |                 |  |

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|---|-----------------|------------------|--|
| subjects affected / exposed                     | 1 / 657 (0.15%) | 1 / 554 (0.18%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Colitis   |                 |                  |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 2 / 554 (0.36%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Crohn's disease                                 |                 |                  |  |
| subjects affected / exposed                     | 2 / 657 (0.30%) | 0 / 554 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Diarrhoea                                       |                 |                  |  |
| subjects affected / exposed                     | 7 / 657 (1.07%) | 15 / 554 (2.71%) |  |
| occurrences causally related to treatment / all | 0 / 7           | 0 / 16           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Diverticulum intestinal                         |                 |                  |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Dyskinesia oesophageal                          |                 |                  |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (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 / 657 (0.30%) | 0 / 554 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Faecaloma                                       |                 |                  |  |
| subjects affected / exposed                     | 2 / 657 (0.30%) | 0 / 554 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Gastric ulcer                                   |                 |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastric ulcer haemorrhage                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastritis                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorder                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal haemorrhage                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 5 / 554 (0.90%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 7           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal obstruction                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematemesis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematochezia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemorrhoids                                    |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ileus   |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Impaired gastric emptying                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Inguinal hernia                                 |                 |                 |  |
| subjects affected / exposed                     | 3 / 657 (0.46%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intestinal infarction                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Intestinal ischaemia                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (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 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Intra-abdominal haematoma                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Large intestine perforation                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 657 (0.15%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Large intestine polyp                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (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                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mesenteritis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nausea  |                 |                 |  |
| subjects affected / exposed                     | 3 / 657 (0.46%) | 3 / 554 (0.54%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neutropenic colitis                             |                 |                 |  |
| subjects affected / exposed                     | 2 / 657 (0.30%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatic insufficiency                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis acute                              |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| 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                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Small intestinal obstruction                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Stomatitis                                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 657 (0.30%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper gastrointestinal haemorrhage              |                 |                 |  |
| subjects affected / exposed                     | 2 / 657 (0.30%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vomiting  |                 |                 |  |
| subjects affected / exposed                     | 4 / 657 (0.61%) | 5 / 554 (0.90%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Bile duct stenosis                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bile duct stone                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholangitis                                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 657 (0.15%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholangitis acute                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholecystitis                                   |                 |                 |  |
| subjects affected / exposed                     | 2 / 657 (0.30%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholecystitis acute                             |                 |                 |  |
| subjects affected / exposed                     | 2 / 657 (0.30%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholelithiasis obstructive                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Granulomatous liver disease                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic cirrhosis                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Hepatic failure                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Hydrocholecystitis                              |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Jaundice  |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Jaundice cholestatic                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Portal hypertension                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| 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          |                 |                 |  |
| Blister   |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dermal cyst                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dermatitis exfoliative                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Eczema  |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rash  |                 |                 |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 1 / 657 (0.15%) | 1 / 554 (0.18%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Rash maculo-papular                             |                 |                  |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Rash vesicular                                  |                 |                  |  |
| subjects affected / exposed                     | 3 / 657 (0.46%) | 3 / 554 (0.54%)  |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Renal and urinary disorders                     |                 |                  |  |
| Acute kidney injury                             |                 |                  |  |
| subjects affected / exposed                     | 8 / 657 (1.22%) | 10 / 554 (1.81%) |  |
| occurrences causally related to treatment / all | 0 / 10          | 0 / 11           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1            |  |
| Acute prerenal failure                          |                 |                  |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 2 / 554 (0.36%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Cystitis haemorrhagic                           |                 |                  |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| End stage renal disease                         |                 |                  |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (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                     | 2 / 657 (0.30%) | 2 / 554 (0.36%)  |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Nephrolithiasis                                 |                 |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal failure                                   |                 |                 |  |
| subjects affected / exposed                     | 4 / 657 (0.61%) | 5 / 554 (0.90%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Renal injury                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal tubular necrosis                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tubulointerstitial nephritis                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ureterolithiasis                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary retention                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Endocrine disorders                             |                 |                 |  |
| Hyperthyroidism                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Arthralgia                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Back pain                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bone pain                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cervical spinal stenosis                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intervertebral disc degeneration                |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intervertebral disc protrusion                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 657 (0.30%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neck pain                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteoarthritis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteolysis                                      |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteonecrosis                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pathological fracture                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pseudarthrosis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal column stenosis                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Abdominal abscess                               |                 |                 |  |
| subjects affected / exposed                     | 2 / 657 (0.30%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Actinomycotic pulmonary infection               |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute sinusitis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Adenovirus infection                            |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Anal abscess                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Appendicitis                                    |                 |                 |  |
| subjects affected / exposed                     | 2 / 657 (0.30%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Appendicitis perforated                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arthritis bacterial                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Aspergilloma                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Aspergillus infection                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atypical pneumonia                              |                 |                 |  |
| subjects affected / exposed                     | 6 / 657 (0.91%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 3           | 0 / 0           |  |
| BK virus infection                              |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Bacteraemia</b>                              |                 |                 |  |
| subjects affected / exposed                     | 4 / 657 (0.61%) | 7 / 554 (1.26%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 8           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| <b>Bacterial sepsis</b>                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Bronchiolitis</b>                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Bronchitis</b>                               |                 |                 |  |
| subjects affected / exposed                     | 4 / 657 (0.61%) | 4 / 554 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Bronchitis bacterial</b>                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Bronchitis viral</b>                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Bronchopulmonary aspergillosis</b>           |                 |                 |  |
| subjects affected / exposed                     | 6 / 657 (0.91%) | 4 / 554 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| <b>Candida sepsis</b>                           |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cellulitis                                      |                 |                 |  |
| subjects affected / exposed                     | 4 / 657 (0.61%) | 3 / 554 (0.54%) |  |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholangitis infective                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic hepatitis B                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Clostridial infection                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Clostridium colitis                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (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                     | 5 / 657 (0.76%) | 5 / 554 (0.90%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Clostridium difficile infection                 |                 |                 |  |
| subjects affected / exposed                     | 3 / 657 (0.46%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coxsackie viral infection                       |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cystitis  |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cytomegalovirus colitis                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Cytomegalovirus infection                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cytomegalovirus oesophagitis                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dengue fever                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Device related infection                        |                 |                 |  |
| subjects affected / exposed                     | 5 / 657 (0.76%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Device related sepsis                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diverticulitis                                  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 3 / 657 (0.46%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Empyema   |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| 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                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enterococcal infection                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enterocolitis bacterial                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enterovirus infection                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Epididymitis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Erysipelas                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Escherichia bacteraemia                         |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 657 (0.30%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Escherichia sepsis                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Escherichia urinary tract infection             |                 |                 |  |
| subjects affected / exposed                     | 3 / 657 (0.46%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Febrile infection                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fungal oesophagitis                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis                                 |                 |                 |  |
| subjects affected / exposed                     | 5 / 657 (0.76%) | 4 / 554 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis rotavirus                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis viral                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal candidiasis                    |                 |                 |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Gastrointestinal infection                      |                 |                  |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Groin abscess                                   |                 |                  |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| H1N1 influenza                                  |                 |                  |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Haemophilus infection                           |                 |                  |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Herpes zoster                                   |                 |                  |  |
| subjects affected / exposed                     | 3 / 657 (0.46%) | 12 / 554 (2.17%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 12           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Herpes zoster disseminated                      |                 |                  |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Infected lymphocele                             |                 |                  |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Infection                                       |                 |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                                   | 1 / 657 (0.15%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Infection in an immunocompromised host                        |                 |                 |  |
| subjects affected / exposed                                   | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Infective exacerbation of chronic obstructive airways disease |                 |                 |  |
| subjects affected / exposed                                   | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all               | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Influenza   |                 |                 |  |
| subjects affected / exposed                                   | 8 / 657 (1.22%) | 7 / 554 (1.26%) |  |
| occurrences causally related to treatment / all               | 0 / 8           | 0 / 7           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Klebsiella bacteraemia  |                 |                 |  |
| subjects affected / exposed                                   | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Klebsiella infection  |                 |                 |  |
| subjects affected / exposed                                   | 1 / 657 (0.15%) | 0 / 554 (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                                   | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all               | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Lower respiratory tract infection viral                       |                 |                 |  |
| subjects affected / exposed                                   | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all               | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Lung abscess  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung infection                                  |                 |                 |  |
| subjects affected / exposed                     | 3 / 657 (0.46%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Lung infection pseudomonal                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Meningitis                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Meningitis pneumococcal                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Meningoencephalitis herpetic                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nasopharyngitis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neutropenic sepsis                              |                 |                 |  |
| subjects affected / exposed                     | 3 / 657 (0.46%) | 3 / 554 (0.54%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 1           |  |
| Oral candidiasis                                |                 |                 |  |



|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 657 (0.15%)  | 1 / 554 (0.18%)   |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Parainfluenzae virus infection                  |                  |                   |  |
| subjects affected / exposed                     | 0 / 657 (0.00%)  | 2 / 554 (0.36%)   |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Pharyngitis                                     |                  |                   |  |
| subjects affected / exposed                     | 2 / 657 (0.30%)  | 0 / 554 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Pneumococcal bacteraemia                        |                  |                   |  |
| subjects affected / exposed                     | 0 / 657 (0.00%)  | 2 / 554 (0.36%)   |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Pneumococcal sepsis                             |                  |                   |  |
| subjects affected / exposed                     | 1 / 657 (0.15%)  | 3 / 554 (0.54%)   |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1             |  |
| Pneumocystis jirovecii infection                |                  |                   |  |
| subjects affected / exposed                     | 1 / 657 (0.15%)  | 0 / 554 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Pneumocystis jirovecii pneumonia                |                  |                   |  |
| subjects affected / exposed                     | 1 / 657 (0.15%)  | 2 / 554 (0.36%)   |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1             |  |
| Pneumonia                                       |                  |                   |  |
| subjects affected / exposed                     | 61 / 657 (9.28%) | 56 / 554 (10.11%) |  |
| occurrences causally related to treatment / all | 0 / 74           | 1 / 67            |  |
| deaths causally related to treatment / all      | 0 / 5            | 0 / 6             |  |
| Pneumonia bacterial                             |                  |                   |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 657 (0.15%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia cytomegaloviral                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia fungal                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Pneumonia parainfluenzae viral                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia respiratory syncytial viral           |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia viral                                 |                 |                 |  |
| subjects affected / exposed                     | 2 / 657 (0.30%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Postoperative abscess                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Postoperative wound infection                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pseudomembranous colitis                        |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 657 (0.15%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pseudomonal bacteraemia                         |                 |                 |  |
| subjects affected / exposed                     | 2 / 657 (0.30%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pseudomonal sepsis                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Pseudomonas infection                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary mycosis                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary sepsis                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| Pulmonary tuberculosis                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory syncytial virus infection           |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory tract infection                     |                 |                 |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 657 (0.30%)  | 0 / 554 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Respiratory tract infection viral               |                  |                  |  |
| subjects affected / exposed                     | 2 / 657 (0.30%)  | 0 / 554 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Retinitis                                       |                  |                  |  |
| subjects affected / exposed                     | 0 / 657 (0.00%)  | 1 / 554 (0.18%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Rhinovirus infection                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 657 (0.00%)  | 1 / 554 (0.18%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Scrotal abscess                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 657 (0.15%)  | 0 / 554 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sepsis  |                  |                  |  |
| subjects affected / exposed                     | 19 / 657 (2.89%) | 12 / 554 (2.17%) |  |
| occurrences causally related to treatment / all | 0 / 19           | 0 / 14           |  |
| deaths causally related to treatment / all      | 0 / 5            | 0 / 3            |  |
| Sepsis syndrome                                 |                  |                  |  |
| subjects affected / exposed                     | 1 / 657 (0.15%)  | 2 / 554 (0.36%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Septic shock                                    |                  |                  |  |
| subjects affected / exposed                     | 7 / 657 (1.07%)  | 4 / 554 (0.72%)  |  |
| occurrences causally related to treatment / all | 0 / 7            | 0 / 4            |  |
| deaths causally related to treatment / all      | 0 / 6            | 0 / 3            |  |
| Sialoadenitis                                   |                  |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sinusitis                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 3 / 554 (0.54%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Staphylococcal bacteraemia                      |                 |                 |  |
| subjects affected / exposed                     | 4 / 657 (0.61%) | 3 / 554 (0.54%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Staphylococcal infection                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Staphylococcal sepsis                           |                 |                 |  |
| subjects affected / exposed                     | 2 / 657 (0.30%) | 4 / 554 (0.72%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Streptococcal bacteraemia                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Streptococcal sepsis                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Systemic candida                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Thrombophlebitis septic                         |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tooth abscess                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tuberculosis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 5 / 657 (0.76%) | 5 / 554 (0.90%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 8 / 657 (1.22%) | 5 / 554 (0.90%) |  |
| occurrences causally related to treatment / all | 0 / 10          | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urosepsis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Varicella                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Varicella zoster virus infection                |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Viral infection                                 |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 657 (0.30%) | 5 / 554 (0.90%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Viral sepsis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Viral upper respiratory tract infection         |                 |                 |  |
| subjects affected / exposed                     | 2 / 657 (0.30%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wound infection bacterial                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Decreased appetite                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dehydration                                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 657 (0.30%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetes mellitus                               |                 |                 |  |
| subjects affected / exposed                     | 2 / 657 (0.30%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Failure to thrive                               |                 |                 |  |
| subjects affected / exposed                     | 3 / 657 (0.46%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 2           | 0 / 0           |  |
| Food intolerance                                |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypercalcaemia                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 657 (0.30%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperglycaemia                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypocalcaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 2 / 554 (0.36%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoglycaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypokalaemia                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lactose intolerance                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tetany  |                 |                 |  |
| subjects affected / exposed                     | 0 / 657 (0.00%) | 1 / 554 (0.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tumour lysis syndrome                           |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 657 (0.15%) | 0 / 554 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 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>                     | V212 [including High Antigen Lot] | Placebo            |  |
|---|-----------------------------------|--------------------|--|
| Total subjects affected by non-serious adverse events |                                   |                    |  |
| subjects affected / exposed                           | 625 / 657 (95.13%)                | 512 / 554 (92.42%) |  |
| Vascular disorders                                    |                                   |                    |  |
| Hypertension  |                                   |                    |  |
| subjects affected / exposed                           | 33 / 657 (5.02%)                  | 33 / 554 (5.96%)   |  |
| occurrences (all)                                     | 38                                | 36                 |  |
| Hypotension   |                                   |                    |  |
| subjects affected / exposed                           | 57 / 657 (8.68%)                  | 48 / 554 (8.66%)   |  |
| occurrences (all)                                     | 64                                | 52                 |  |
| Cardiac disorders                                     |                                   |                    |  |
| Tachycardia   |                                   |                    |  |
| subjects affected / exposed                           | 45 / 657 (6.85%)                  | 34 / 554 (6.14%)   |  |
| occurrences (all)                                     | 47                                | 35                 |  |
| Nervous system disorders                              |                                   |                    |  |
| Dizziness   |                                   |                    |  |
| subjects affected / exposed                           | 44 / 657 (6.70%)                  | 46 / 554 (8.30%)   |  |
| occurrences (all)                                     | 46                                | 51                 |  |
| Dysgeusia   |                                   |                    |  |
| subjects affected / exposed                           | 29 / 657 (4.41%)                  | 28 / 554 (5.05%)   |  |
| occurrences (all)                                     | 29                                | 28                 |  |
| Headache  |                                   |                    |  |
| subjects affected / exposed                           | 131 / 657 (19.94%)                | 114 / 554 (20.58%) |  |
| occurrences (all)                                     | 149                               | 141                |  |
| Blood and lymphatic system disorders                  |                                   |                    |  |
| Anaemia   |                                   |                    |  |
| subjects affected / exposed                           | 175 / 657 (26.64%)                | 134 / 554 (24.19%) |  |
| occurrences (all)                                     | 201                               | 168                |  |
| Febrile neutropenia                                   |                                   |                    |  |

|  |                    |                    |  |
|--|--------------------|--------------------|--|
| subjects affected / exposed                          | 184 / 657 (28.01%) | 135 / 554 (24.37%) |  |
| occurrences (all)                                    | 191                | 138                |  |
| Leukopenia   |                    |                    |  |
| subjects affected / exposed                          | 33 / 657 (5.02%)   | 32 / 554 (5.78%)   |  |
| occurrences (all)                                    | 34                 | 41                 |  |
| Neutropenia  |                    |                    |  |
| subjects affected / exposed                          | 163 / 657 (24.81%) | 129 / 554 (23.29%) |  |
| occurrences (all)                                    | 187                | 157                |  |
| Pancytopenia   |                    |                    |  |
| subjects affected / exposed                          | 63 / 657 (9.59%)   | 53 / 554 (9.57%)   |  |
| occurrences (all)                                    | 64                 | 54                 |  |
| Thrombocytopenia                                     |                    |                    |  |
| subjects affected / exposed                          | 238 / 657 (36.23%) | 212 / 554 (38.27%) |  |
| occurrences (all)                                    | 289                | 264                |  |
| General disorders and administration site conditions |                    |                    |  |
| Asthenia   |                    |                    |  |
| subjects affected / exposed                          | 72 / 657 (10.96%)  | 60 / 554 (10.83%)  |  |
| occurrences (all)                                    | 77                 | 68                 |  |
| Chills   |                    |                    |  |
| subjects affected / exposed                          | 39 / 657 (5.94%)   | 35 / 554 (6.32%)   |  |
| occurrences (all)                                    | 44                 | 42                 |  |
| Fatigue  |                    |                    |  |
| subjects affected / exposed                          | 144 / 657 (21.92%) | 121 / 554 (21.84%) |  |
| occurrences (all)                                    | 159                | 131                |  |
| Injection site erythema                              |                    |                    |  |
| subjects affected / exposed                          | 153 / 657 (23.29%) | 14 / 554 (2.53%)   |  |
| occurrences (all)                                    | 323                | 19                 |  |
| Injection site pain                                  |                    |                    |  |
| subjects affected / exposed                          | 133 / 657 (20.24%) | 21 / 554 (3.79%)   |  |
| occurrences (all)                                    | 283                | 24                 |  |
| Injection site pruritus                              |                    |                    |  |
| subjects affected / exposed                          | 35 / 657 (5.33%)   | 4 / 554 (0.72%)    |  |
| occurrences (all)                                    | 52                 | 5                  |  |
| Injection site swelling                              |                    |                    |  |

|                             |                    |                    |  |
|-----------------------------|--------------------|--------------------|--|
| subjects affected / exposed | 124 / 657 (18.87%) | 9 / 554 (1.62%)    |  |
| occurrences (all)           | 257                | 9                  |  |
| Mucosal inflammation        |                    |                    |  |
| subjects affected / exposed | 254 / 657 (38.66%) | 226 / 554 (40.79%) |  |
| occurrences (all)           | 271                | 244                |  |
| Oedema peripheral           |                    |                    |  |
| subjects affected / exposed | 77 / 657 (11.72%)  | 65 / 554 (11.73%)  |  |
| occurrences (all)           | 89                 | 72                 |  |
| Pyrexia                     |                    |                    |  |
| subjects affected / exposed | 317 / 657 (48.25%) | 248 / 554 (44.77%) |  |
| occurrences (all)           | 526                | 374                |  |
| Gastrointestinal disorders  |                    |                    |  |
| Abdominal pain              |                    |                    |  |
| subjects affected / exposed | 87 / 657 (13.24%)  | 78 / 554 (14.08%)  |  |
| occurrences (all)           | 103                | 81                 |  |
| Abdominal pain upper        |                    |                    |  |
| subjects affected / exposed | 51 / 657 (7.76%)   | 34 / 554 (6.14%)   |  |
| occurrences (all)           | 51                 | 35                 |  |
| Constipation                |                    |                    |  |
| subjects affected / exposed | 107 / 657 (16.29%) | 102 / 554 (18.41%) |  |
| occurrences (all)           | 120                | 113                |  |
| Diarrhoea                   |                    |                    |  |
| subjects affected / exposed | 394 / 657 (59.97%) | 341 / 554 (61.55%) |  |
| occurrences (all)           | 492                | 396                |  |
| Dyspepsia                   |                    |                    |  |
| subjects affected / exposed | 61 / 657 (9.28%)   | 47 / 554 (8.48%)   |  |
| occurrences (all)           | 65                 | 52                 |  |
| Nausea                      |                    |                    |  |
| subjects affected / exposed | 370 / 657 (56.32%) | 319 / 554 (57.58%) |  |
| occurrences (all)           | 452                | 391                |  |
| Stomatitis                  |                    |                    |  |
| subjects affected / exposed | 83 / 657 (12.63%)  | 51 / 554 (9.21%)   |  |
| occurrences (all)           | 94                 | 56                 |  |
| Vomiting                    |                    |                    |  |
| subjects affected / exposed | 211 / 657 (32.12%) | 200 / 554 (36.10%) |  |
| occurrences (all)           | 265                | 260                |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| Respiratory, thoracic and mediastinal disorders |                   |                   |  |
| Cough   |                   |                   |  |
| subjects affected / exposed                     | 76 / 657 (11.57%) | 80 / 554 (14.44%) |  |
| occurrences (all)                               | 84                | 93                |  |
| Dyspnoea  |                   |                   |  |
| subjects affected / exposed                     | 55 / 657 (8.37%)  | 36 / 554 (6.50%)  |  |
| occurrences (all)                               | 60                | 36                |  |
| Epistaxis                                       |                   |                   |  |
| subjects affected / exposed                     | 41 / 657 (6.24%)  | 24 / 554 (4.33%)  |  |
| occurrences (all)                               | 48                | 26                |  |
| Oropharyngeal pain                              |                   |                   |  |
| subjects affected / exposed                     | 68 / 657 (10.35%) | 43 / 554 (7.76%)  |  |
| occurrences (all)                               | 78                | 48                |  |
| Skin and subcutaneous tissue disorders          |                   |                   |  |
| Erythema  |                   |                   |  |
| subjects affected / exposed                     | 33 / 657 (5.02%)  | 22 / 554 (3.97%)  |  |
| occurrences (all)                               | 37                | 31                |  |
| Pruritus  |                   |                   |  |
| subjects affected / exposed                     | 66 / 657 (10.05%) | 38 / 554 (6.86%)  |  |
| occurrences (all)                               | 72                | 45                |  |
| Rash  |                   |                   |  |
| subjects affected / exposed                     | 89 / 657 (13.55%) | 74 / 554 (13.36%) |  |
| occurrences (all)                               | 110               | 84                |  |
| Psychiatric disorders                           |                   |                   |  |
| Anxiety   |                   |                   |  |
| subjects affected / exposed                     | 35 / 657 (5.33%)  | 31 / 554 (5.60%)  |  |
| occurrences (all)                               | 38                | 32                |  |
| Insomnia  |                   |                   |  |
| subjects affected / exposed                     | 84 / 657 (12.79%) | 68 / 554 (12.27%) |  |
| occurrences (all)                               | 91                | 71                |  |
| Musculoskeletal and connective tissue disorders |                   |                   |  |
| Back pain                                       |                   |                   |  |
| subjects affected / exposed                     | 56 / 657 (8.52%)  | 46 / 554 (8.30%)  |  |
| occurrences (all)                               | 63                | 51                |  |
| Pain in extremity                               |                   |                   |  |

|  |                        |                        |  |
|--|------------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all) | 33 / 657 (5.02%)<br>35 | 24 / 554 (4.33%)<br>26 |  |
| Metabolism and nutrition disorders               |                        |                        |  |
| Decreased appetite                               |                        |                        |  |
| subjects affected / exposed                      | 152 / 657 (23.14%)     | 132 / 554 (23.83%)     |  |
| occurrences (all)                                | 161                    | 150                    |  |
| Hyperglycaemia                                   |                        |                        |  |
| subjects affected / exposed                      | 33 / 657 (5.02%)       | 16 / 554 (2.89%)       |  |
| occurrences (all)                                | 40                     | 16                     |  |
| Hypocalcaemia                                    |                        |                        |  |
| subjects affected / exposed                      | 55 / 657 (8.37%)       | 40 / 554 (7.22%)       |  |
| occurrences (all)                                | 65                     | 45                     |  |
| Hypokalaemia                                     |                        |                        |  |
| subjects affected / exposed                      | 141 / 657 (21.46%)     | 111 / 554 (20.04%)     |  |
| occurrences (all)                                | 165                    | 135                    |  |
| Hypomagnesaemia                                  |                        |                        |  |
| subjects affected / exposed                      | 76 / 657 (11.57%)      | 62 / 554 (11.19%)      |  |
| occurrences (all)                                | 88                     | 75                     |  |
| Hypophosphataemia                                |                        |                        |  |
| subjects affected / exposed                      | 41 / 657 (6.24%)       | 40 / 554 (7.22%)       |  |
| occurrences (all)                                | 48                     | 42                     |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment   |
|-----------------|---|
| 09 July 2010    | Amendment 1: The primary reasons for this amendment are to change the pre-specified criteria for success for the primary efficacy hypothesis and to elevate critical exploratory efficacy endpoints to secondary efficacy endpoints.  |
| 13 October 2010 | Amendment 2: The primary clinical efficacy endpoint was modified to exclude recipients of inactivated VZV vaccine High Antigen Lot. Therefore, the primary clinical efficacy endpoint included the incidence of HZ among the inactivated VZV Consistency Lot 1, 2, 3 and placebo recipients only.   |
| 02 January 2013 | Amendment 4: The following text was added, anticipating that an original vaccine lot might expire prior to all participants completing their 4-dose regimen: A given participant is anticipated to receive all 4 doses in the series from the same lot. In the event that the vaccine lot expires prior to a participant receiving all 4 doses of study vaccine, doses will be administered from a new lot of comparable antigen content. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date              | Interruption  | Restart date    |
|-------------------|---|-----------------|
| 22 September 2012 | The Data Monitoring Committee temporarily paused enrollment and vaccination to evaluate preliminary reports of disseminated rash lesions that tested PCR positive for VZV Oka/Merck (vaccine strain) in another V212 study. The available evidence suggested that these PCR results were likely false positive. | 02 October 2012 |

Notes:

### Limitations and caveats

None reported