



## Clinical trial results:

### A Randomized, Double-Blind, Placebo-Controlled, Phase 3 Trial to Evaluate the Protective Efficacy and Safety of a Therapeutic Vaccine, ASP0113, in Cytomegalovirus (CMV)-Seropositive Recipients Undergoing Allogeneic, Hematopoietic Cell Transplant (HCT)

#### Summary

|                          |                |
|--------------------------|----------------|
| EudraCT number           | 2013-000903-18 |
| Trial protocol           | SE DE BE ES    |
| Global end of trial date | 01 March 2022  |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v2 (current)    |
| This version publication date  | 27 October 2022 |
| First version publication date | 03 October 2018 |
| Version creation reason        |                 |

#### Trial information

##### Trial identification

|                       |              |
|-----------------------|--------------|
| Sponsor protocol code | 0113-CL-1004 |
|-----------------------|--------------|

##### Additional study identifiers

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT01877655 |
| WHO universal trial number (UTN)   | -           |

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Astellas Pharma Global Development US  |
| Sponsor organisation address | 1 Astellas Way, Northbrook, United States,   |
| Public contact               | Clinical Trial Disclosure, Astellas Pharma Global Development US, 001 800-888-7704 ex 5473, <a href="mailto:astellas.resultsdisclosure@astellas.com">astellas.resultsdisclosure@astellas.com</a> |
| Scientific contact           | Clinical Trial Disclosure, Astellas Pharma Global Development US, 001 800-888-7704 ex 5473, <a href="mailto:astellas.resultsdisclosure@astellas.com">astellas.resultsdisclosure@astellas.com</a> |

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                                       | Interim           |
| Date of interim/final analysis                       | 28 September 2017 |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 28 September 2017 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 01 March 2022     |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate efficacy of ASP0113 compared with placebo as measured by a primary composite endpoint of overall mortality and cytomegalovirus end organ disease (CMV EOD) through 1 year posttransplant and to evaluate safety of ASP0113 in participants undergoing allogeneic hematopoietic cell transplant (HCT).

Protection of trial subjects:

This clinical study was written, conducted and reported in accordance with the protocol, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) Good Clinical Practice (GCP) Guidelines, and applicable local regulations, including the European Directive 2001/20/EC, on the protection of human rights, and with the ethical principles that have their origin in the Declaration of Helsinki. Astellas ensures that the use and disclosure of protected health information (PHI) obtained during a research study complies with the federal, national and/or regional legislation related to the privacy and protection of personal information.

Background therapy:

All concomitant medications and therapies administered from 30 days prior to transplant through 30 days after the last dose of study drug were recorded on the eCRF. From 31 days after the last dose of study drug through 1 year posttransplant, concomitant medications and therapies associated with all events required adjudication.

Evidence for comparator: -

|   |                   |
|---|-------------------|
| Actual start date of recruitment                          | 11 September 2013 |
| Long term follow-up planned                               | Yes               |
| Long term follow-up rationale                             | Safety            |
| Long term follow-up duration                              | 54 Months         |
| Independent data monitoring committee (IDMC) involvement? | Yes               |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Australia: 5           |
| Country: Number of subjects enrolled | Belgium: 47            |
| Country: Number of subjects enrolled | Canada: 15             |
| Country: Number of subjects enrolled | France: 30             |
| Country: Number of subjects enrolled | Germany: 54            |
| Country: Number of subjects enrolled | Japan: 47              |
| Country: Number of subjects enrolled | Korea, Republic of: 23 |
| Country: Number of subjects enrolled | Spain: 75              |
| Country: Number of subjects enrolled | Sweden: 31             |
| Country: Number of subjects enrolled | Taiwan: 17             |
| Country: Number of subjects enrolled | United States: 170     |

|                                    |     |
|------------------------------------|-----|
| Worldwide total number of subjects | 514 |
| EEA total number of subjects       | 237 |

Notes:

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### Subjects enrolled per age group

---

|   |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 431 |
| From 65 to 84 years                       | 83  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

A total of 514 participants were enrolled across 11 countries. At least 30% of enrolled participants had CMV seronegative donor and underwent allogeneic HCT. After primary study period (day 365) 326 participants entered the long-term follow-up period and were monitored for 5.5 years post-transplant for long-term safety.

### Pre-assignment

Screening details:

Screening assessment occurred from 30 to 5 days before transplant. Participants who met the inclusion and none of the exclusion criteria were randomly assigned in a 1:1 ratio to receive either ASP0113 or placebo. The randomization to treatment was stratified by donor-recipient relatedness and by donor CMV serostatus.

### 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, Carer, Assessor |

Blinding implementation details:

Study drug assignment was blinded to all site staff except the pharmacist, designated staff and the unblinded administrator.

### Arms

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

Arm description:

Participants received 1 mL of 5 mg/mL of matching placebo via intramuscular injection in the deltoid muscle alternating sides with each dose on days -14 to -3 pretransplant, 14 to 40, 60, 90 and 180 in relation to the day of transplant (Day 0).

|  |                   |
|--|-------------------|
| Arm type                               | Placebo           |
| Investigational medicinal product name | Placebo           |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Injection         |
| Routes of administration               | Intramuscular use |

Dosage and administration details:

Participants received matching placebo in 2-mL vials containing phosphate-buffered saline.

|                  |             |
|------------------|-------------|
| <b>Arm title</b> | ASP0113 5mg |
|------------------|-------------|

Arm description:

Participants received 1 mL of 5 mg/mL of ASP0113 via intramuscular injection in the deltoid muscle alternating sides with each dose on days -14 to -3 pretransplant, 14 to 40, 60, 90 and 180 in relation to the day of transplant (Day 0).

|  |                   |
|--|-------------------|
| Arm type                               | Experimental      |
| Investigational medicinal product name | ASP0113           |
| Investigational medicinal product code |                   |
| Other name                             |                   |
| Pharmaceutical forms                   | Injection         |
| Routes of administration               | Intramuscular use |

Dosage and administration details:

Participants received ASP0113 in single-dose 2-mL vials containing 1.3 mL of 5 mg/mL ASP0113.

| <b>Number of subjects in period 1</b> | Placebo | ASP0113 5mg |
|---------------------------------------|---------|-------------|
| Started                               | 263     | 251         |
| Received Treatment                    | 255     | 246         |
| Completed                             | 165     | 154         |
| Not completed                         | 98      | 97          |
| Consent withdrawn by subject          | 18      | 26          |
| Physician decision                    | 11      | 10          |
| Death                                 | 57      | 52          |
| Miscellaneous                         | 4       | 4           |
| Randomized but Never Received Drug    | 8       | 5           |

## Baseline characteristics

### Reporting groups

|  |             |
|--|-------------|
| Reporting group title  | Placebo     |
| Reporting group description:   |             |
| Participants received 1 mL of 5 mg/mL of matching placebo via intramuscular injection in the deltoid muscle alternating sides with each dose on days -14 to -3 pretransplant, 14 to 40, 60, 90 and 180 in relation to the day of transplant (Day 0). |             |
| Reporting group title  | ASP0113 5mg |
| Reporting group description:   |             |
| Participants received 1 mL of 5 mg/mL of ASP0113 via intramuscular injection in the deltoid muscle alternating sides with each dose on days -14 to -3 pretransplant, 14 to 40, 60, 90 and 180 in relation to the day of transplant (Day 0).          |             |

| Reporting group values | Placebo | ASP0113 5mg | Total |
|------------------------|---------|-------------|-------|
| Number of subjects     | 263     | 251         | 514   |
| Age categorical        |         |             |       |
| Units: Subjects        |         |             |       |

|   |         |         |     |
|---|---------|---------|-----|
| Age continuous                            |         |         |     |
| Units: years                              |         |         |     |
| arithmetic mean                           | 52.0    | 51.8    |     |
| standard deviation                        | ± 13.15 | ± 12.41 | -   |
| Gender categorical                        |         |         |     |
| Units: Subjects                           |         |         |     |
| Female                                    | 105     | 110     | 215 |
| Male                                      | 158     | 141     | 299 |
| Race (NIH/OMB)                            |         |         |     |
| Units: Subjects                           |         |         |     |
| American Indian or Alaska Native          | 0       | 0       | 0   |
| Asian                                     | 47      | 50      | 97  |
| Native Hawaiian or Other Pacific Islander | 0       | 0       | 0   |
| Black or African American                 | 6       | 7       | 13  |
| White                                     | 189     | 177     | 366 |
| More than one race                        | 0       | 0       | 0   |
| Unknown or Not Reported                   | 21      | 17      | 38  |
| Strata                                    |         |         |     |
| Units: Subjects                           |         |         |     |
| Related Seropositive Donor                | 65      | 73      | 138 |
| Related Seronegative Donor                | 30      | 26      | 56  |
| Non-related Seropositive Donor            | 96      | 73      | 169 |
| Non-related Seronegative Donor            | 72      | 79      | 151 |
| Primary Diagnosis                         |         |         |     |
| Units: Subjects                           |         |         |     |
| Acute Myeloid Leukemia (AML)              | 126     | 97      | 223 |
| Acute Lymphoblastic Leukemia (ALL)        | 34      | 34      | 68  |
| Acute Undifferentiated Leukemia (AUL)     | 1       | 2       | 3   |
| Acute Biphennotypic Leukemia (ABL)        | 2       | 2       | 4   |

|                                    |        |        |     |
|------------------------------------|--------|--------|-----|
| Chronic Myelogenous Leukemia (CML) | 6      | 12     | 18  |
| Chronic Lymphocytic Leukemia (CLL) | 7      | 10     | 17  |
| Myelodysplastic Syndrome           | 46     | 51     | 97  |
| Primary or Secondary Myelofibrosis | 8      | 11     | 19  |
| Lymphoma                           | 33     | 31     | 64  |
| Missing                            | 0      | 1      | 1   |
| Conditioning Regimen               |        |        |     |
| Units: Subjects                    |        |        |     |
| Myeloablative                      | 122    | 120    | 242 |
| Non-Myeloablative                  | 131    | 124    | 255 |
| Missing                            | 10     | 7      | 17  |
| Antithymocyte Globulin (ATG) Use   |        |        |     |
| Units: Subjects                    |        |        |     |
| ATG Use Yes                        | 45     | 43     | 88  |
| ATG Use No                         | 218    | 208    | 426 |
| Ethnicity                          |        |        |     |
| Units: Subjects                    |        |        |     |
| Hispanic or Latino                 | 11     | 19     | 30  |
| Not Hispanic or Latino             | 252    | 232    | 484 |
| Height                             |        |        |     |
| Units: Centimeteres                |        |        |     |
| arithmetic mean                    | 170.6  | 169.7  |     |
| standard deviation                 | ± 9.91 | ± 9.88 | -   |
| Body Mass Index (BMI)              |        |        |     |
| Units: kg/m^2                      |        |        |     |
| arithmetic mean                    | 27.0   | 26.0   |     |
| standard deviation                 | ± 5.02 | ± 5.05 | -   |

## End points

### End points reporting groups

|  |             |
|--|-------------|
| Reporting group title  | Placebo     |
| Reporting group description:<br>Participants received 1 mL of 5 mg/mL of matching placebo via intramuscular injection in the deltoid muscle alternating sides with each dose on days -14 to -3 pretransplant, 14 to 40, 60, 90 and 180 in relation to the day of transplant (Day 0). |             |
| Reporting group title  | ASP0113 5mg |
| Reporting group description:<br>Participants received 1 mL of 5 mg/mL of ASP0113 via intramuscular injection in the deltoid muscle alternating sides with each dose on days -14 to -3 pretransplant, 14 to 40, 60, 90 and 180 in relation to the day of transplant (Day 0).          |             |

### Primary: Percentage of Participants With Composite of All-Cause Mortality and Adjudicated Cytomegalovirus End Organ Disease (CMV EOD) Through 1 Year Post Transplant

|  |   |
|--|---|
| End point title  | Percentage of Participants With Composite of All-Cause Mortality and Adjudicated Cytomegalovirus End Organ Disease (CMV EOD) Through 1 Year Post Transplant |
| End point description:<br>This was the composite of all-cause mortality and adjudicated CMV EOD through 1 year posttransplant, The CMV EOD was assessed by the independent and blinded adjudication committee, which counted events that were observed up to day 380 from transplantation. Deaths that occurred up to day 365 from transplant were also counted. |   |
| End point type   | Primary   |
| End point timeframe:<br>From first study dose injection (Day -14 to -3 prior to transplant) up to one year post study drug injection (Day 365)   |   |

| End point values                     | Placebo         | ASP0113 5mg     |  |  |
|--------------------------------------|-----------------|-----------------|--|--|
| Subject group type                   | Reporting group | Reporting group |  |  |
| Number of subjects analysed          | 255             | 246             |  |  |
| Units: Percentage of Participants    |                 |                 |  |  |
| number (not applicable)              |                 |                 |  |  |
| Participants With Composite Endpoint | 30.20           | 35.37           |  |  |
| All-Cause Mortality                  | 28.24           | 31.71           |  |  |
| Adjudicated CMV EOD                  | 3.53            | 6.10            |  |  |

### Statistical analyses

|  |   |
|--|---|
| Statistical analysis title   | All-Cause Mortality and Adjudicated CMV EOD |
| Statistical analysis description:<br>Analysis was completed using the Cochran-Mantel-Haenszel (CMH) test at the 1-sided 5% level stratified by use of antithymocyte globulin (ATG) and by receipt of a kidney from a living or deceased donor. |   |
| Comparison groups  | Placebo v ASP0113 5mg                       |



|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 501                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | = 0.205 <sup>[1]</sup>  |
| Method                                  | Cochran-Mantel-Haenszel |
| Parameter estimate                      | Odds ratio (OR)         |
| Point estimate                          | 1.27                    |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 0.87                    |
| upper limit                             | 1.85                    |

Notes:

[1] - P-value based on CMH general association test stratified by donor-recipient relatedness and donor CMV serostatus.

### Secondary: Percentage of Participants With Protocol-Defined CMV Viremia Through 1 Year Posttransplant

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants With Protocol-Defined CMV Viremia Through 1 Year Posttransplant |
|-----------------|--|

End point description:

Protocol-defined CMV viremia was defined as a CMV plasma viral load  $\geq 1000$  IU/mL as assessed by the central laboratory. Rate was based on cumulative incidence function estimated at 1 year. The central laboratory had the lower limit of quantification [LLOQ] for CMV viral load assessment, so when the viral load was below the LLOQ the actual viral load reading was not possible and was denoted as  $\leq$ LLOQ. If participant had any CMV viral load assessments greater than the LLOQ it was classified as viremic.

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

End point timeframe:

From first study dose injection (Day -14 to -3 prior to transplant) up to one year post study drug injection (Day 365)

| End point values                  | Placebo             | ASP0113 5mg         |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 255                 | 246                 |  |  |
| Units: Percentage of Participants |                     |                     |  |  |
| number (confidence interval 95%)  | 58.6 (52.0 to 64.6) | 56.7 (50.1 to 62.8) |  |  |

### Statistical analyses

|                            |   |
|----------------------------|---|
| Statistical analysis title | CMV Viremia Through 1 Yr Posttransplant |
|----------------------------|---|

Statistical analysis description:

CMV viremia was defined by the protocol as CMV plasma viral load  $\geq 1000$  IU/mL as assessed by the central laboratory. The 95% CI was based on cumulative incidence function CMV viremia rate at 1 year.

|                   |                       |
|-------------------|-----------------------|
| Comparison groups | Placebo v ASP0113 5mg |
|-------------------|-----------------------|

|   |                               |
|---|-------------------------------|
| Number of subjects included in analysis | 501                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | superiority                   |
| P-value                                 | = 0.748 <sup>[2]</sup>        |
| Method                                  | Cox Proportional Hazard Model |
| Parameter estimate                      | Hazard ratio (HR)             |
| Point estimate                          | 0.96                          |
| Confidence interval                     |                               |
| level                                   | 95 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | 0.76                          |
| upper limit                             | 1.22                          |

Notes:

[2] - P-value based on cox proportional hazard model (ASP0113 v placebo) with treatment & randomization strata adjusted for death as a competing risk.

### Secondary: Percentage of Participants With Adjudicated CMV-Specific Antiviral Therapy (AVT) Through 1 Year Posttransplant

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants With Adjudicated CMV-Specific Antiviral Therapy (AVT) Through 1 Year Posttransplant |
|-----------------|--|

End point description:

The CMV-specific AVT use was adjudicated by the independent and blinded committee. When the CMV-specific AVT was initiated, a central CMV viral load was obtained weekly until it was discontinued. Participants without any CMV-specific AVT events were censored on the last study evaluation.

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

End point timeframe:

From first study dose injection (Day -14 to -3 prior to transplant) up to one year post study drug injection (Day 365)

| End point values                  | Placebo             | ASP0113 5mg         |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 255                 | 246                 |  |  |
| Units: Percentage of Participants |                     |                     |  |  |
| number (confidence interval 95%)  | 53.2 (46.8 to 59.1) | 54.6 (48.1 to 60.6) |  |  |

### Statistical analyses

|                            |   |
|----------------------------|---|
| Statistical analysis title | CMV-Specific Antiviral Therapy (AVT) Through 1 Yr |
|----------------------------|---|

Statistical analysis description:

Time to first adjudicated CMV-specific therapy was defined as time to the start of AVT for CMV viremia. CMV-specific AVT was determined by the adjudication committee.

|                   |                       |
|-------------------|-----------------------|
| Comparison groups | Placebo v ASP0113 5mg |
|-------------------|-----------------------|

|   |                               |
|---|-------------------------------|
| Number of subjects included in analysis | 501                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | superiority                   |
| P-value                                 | = 0.888 <sup>[3]</sup>        |
| Method                                  | Cox Proportional Hazard Model |
| Parameter estimate                      | Hazard ratio (HR)             |
| Point estimate                          | 1.02                          |
| Confidence interval                     |                               |
| level                                   | 95 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | 0.8                           |
| upper limit                             | 1.29                          |

Notes:

[3] - P-value based on cox proportional hazard model (ASP0113 v placebo) with treatment & randomization strata adjusted for death as a competing risk.

### Secondary: Percentage of Participants With a Composite Endpoint of Protocol-defined CMV Viremia and Adjudicated CMV-Specific AVT Use

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants With a Composite Endpoint of Protocol-defined CMV Viremia and Adjudicated CMV-Specific AVT Use |
|-----------------|---|

End point description:

Protocol-defined CMV Viremia was as CMV plasma viral load  $\geq 1000$  IU/mL as assessed by the central laboratory. The CMV-specific AVT was determined by the adjudication committee. Participants with no posttransplant viral load data were excluded from the analysis.

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

End point timeframe:

From first study dose injection (Day -14 to -3 prior to transplant) up to one year post study drug injection (Day 365)

| End point values                  | Placebo         | ASP0113 5mg     |  |  |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type                | Reporting group | Reporting group |  |  |
| Number of subjects analysed       | 255             | 246             |  |  |
| Units: Percentage of Participants |                 |                 |  |  |
| number (not applicable)           | 60.78           | 60.98           |  |  |

### Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | Composite of CMV Viremia and Adjudicated CMV-AVT |
|----------------------------|--|

Statistical analysis description:

CMV viremia was defined by the protocol as CMV plasma viral load  $\geq 1000$  IU/mL as assessed by the central laboratory. CMV-specific AVT was determined by the adjudication committee. Patients with no posttransplant viral load data were excluded from the analysis.

|                   |                       |
|-------------------|-----------------------|
| Comparison groups | Placebo v ASP0113 5mg |
|-------------------|-----------------------|

|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 501                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | = 0.802 <sup>[4]</sup>  |
| Method                                  | Cochran-Mantel-Haenszel |
| Parameter estimate                      | Odds ratio (OR)         |
| Point estimate                          | 1.05                    |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 0.73                    |
| upper limit                             | 1.51                    |

Notes:

[4] - P-value based on CMH general association test stratified by donor-recipient relatedness and donor CMV serostatus.

### **Secondary: Percentage of Participants With First Occurrence of Adjudicated CMV-specific AVT or Adjudicated Diagnosis of CMV EOD After Study Drug First Injection Through 1 Year Posttransplant**

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants With First Occurrence of Adjudicated CMV-specific AVT or Adjudicated Diagnosis of CMV EOD After Study Drug First Injection Through 1 Year Posttransplant |
|-----------------|---|

End point description:

Rate was based on cumulative incidence function estimate at 1 year. Time to first CMV-specific AVT was defined as time to the start of AVT for CMV viremia or CMV EOD. CMV-specific AVT and EOD were determined by the adjudication committee. This endpoint was a composite endpoint based on the independent adjudication committee assessments of CMV-specific AVT and CMV EOD.

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

End point timeframe:

From first study dose injection (Day -14 to -3 prior to transplant) up to one year post study drug injection (Day 365)

| <b>End point values</b>           | Placebo             | ASP0113 5mg         |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 255                 | 246                 |  |  |
| Units: Percentage of Participants |                     |                     |  |  |
| number (confidence interval 95%)  | 54.4 (48.0 to 60.3) | 55.4 (48.9 to 61.5) |  |  |

### **Statistical analyses**

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Rate of Adjudicated CMV AVT or CMV EOD |
|-----------------------------------|--|

Statistical analysis description:

Time to first CMV-specific AVT defined as time to the start of AVT for CMV viremia or CMV EOD. CMV-specific AVT and EOD were determined by the adjudication committee. Rate based on cumulative incidence function estimate at 1 year.

|                   |                       |
|-------------------|-----------------------|
| Comparison groups | Placebo v ASP0113 5mg |
|-------------------|-----------------------|

|   |                               |
|---|-------------------------------|
| Number of subjects included in analysis | 501                           |
| Analysis specification                  | Pre-specified                 |
| Analysis type                           | superiority                   |
| P-value                                 | = 0.928 <sup>[5]</sup>        |
| Method                                  | Cox Proportional Hazard Model |
| Parameter estimate                      | Hazard ratio (HR)             |
| Point estimate                          | 1.01                          |
| Confidence interval                     |                               |
| level                                   | 95 %                          |
| sides                                   | 2-sided                       |
| lower limit                             | 0.8                           |
| upper limit                             | 1.28                          |

Notes:

[5] - P-value based on cox proportional hazard model (ASP0113 v placebo) with treatment & randomization strata adjusted for death as a competing risk.

## Secondary: All-Cause Mortality at 1 Year Posttransplant

|                        |   |
|------------------------|---|
| End point title        | All-Cause Mortality at 1 Year Posttransplant  |
| End point description: | All-cause mortality through 1-year post-transplantation summary included all deaths and unknown survival status. For the known deaths, the adjudication committee assessed results and summarized them according to the following category: Mortality due to the participant's primary disease, and Mortality due to causes unrelated to the participant's primary disease. Participants with unknown survival status at 1 year were considered dead for this analysis. |
| End point type         | Secondary   |
| End point timeframe:   | From first study dose injection (Day -14 to -3 prior to transplant) up to one year post study drug injection (Day 365)  |

| End point values                  | Placebo         | ASP0113 5mg     |  |  |
|-----------------------------------|-----------------|-----------------|--|--|
| Subject group type                | Reporting group | Reporting group |  |  |
| Number of subjects analysed       | 255             | 246             |  |  |
| Units: Percentage of Participants |                 |                 |  |  |
| number (not applicable)           | 28.24           | 31.71           |  |  |

## Statistical analyses

|   |   |
|---|---|
| Statistical analysis title              | All-Cause Mortality at 1 Year   |
| Statistical analysis description:       | Participants with unknown survival status at 1 year were considered dead for this analysis. |
| Comparison groups                       | Placebo v ASP0113 5mg   |
| Number of subjects included in analysis | 501   |
| Analysis specification                  | Pre-specified   |
| Analysis type                           | superiority   |
| P-value                                 | = 0.393 <sup>[6]</sup>  |
| Method                                  | Cox Proportional Hazards Model  |
| Parameter estimate                      | Odds ratio (OR)   |
| Point estimate                          | 1.18  |

| Confidence interval |         |
|---------------------|---------|
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.81    |
| upper limit         | 1.73    |

Notes:

[6] - P-value based on cox proportional hazards model parameter estimate for the treatment effect.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Number of Deaths: Baseline up to 5.5 years post transplant.

Adverse Events: From first dose of study drug up to 30 days after last dose of study drug (Day 365).

Adverse event reporting additional description:

TEAE was defined as an AE observed after the first dose of study drug injection through Day 365 and within 30 days of the last dose of study drug. Drug-related TEAE was defined as any TEAE with possible relationship to study treatment as assessed by the investigator. AE data was not planned to be collected during the long-term follow-up period.

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

### Dictionary used

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

|                    |    |
|--------------------|----|
| Dictionary version | 16 |
|--------------------|----|

### Reporting groups

|                       |             |
|-----------------------|-------------|
| Reporting group title | ASP0113 5mg |
|-----------------------|-------------|

Reporting group description:

Participants received 1 mL of 5 mg/mL of ASP0113 via intramuscular injection in the deltoid muscle alternating sides with each dose on days -14 to -3 pretransplant, 14 to 40, 60, 90 and 180 in relation to the day of transplant (Day 0).

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

Reporting group description:

Participants received 1 mL of 5 mg/mL of matching placebo via intramuscular injection in the deltoid muscle alternating sides with each dose on days -14 to -3 pretransplant, 14 to 40, 60, 90 and 180 in relation to the day of transplant (Day 0).

| Serious adverse events  | ASP0113 5mg        | Placebo            |  |
|---|--------------------|--------------------|--|
| Total subjects affected by serious adverse events                   |                    |                    |  |
| subjects affected / exposed   | 221 / 246 (89.84%) | 221 / 255 (86.67%) |  |
| number of deaths (all causes)                                       | 105                | 100                |  |
| number of deaths resulting from adverse events                      | 61                 | 63                 |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |                    |  |
| Acute lymphocytic leukaemia recurrent                               |                    |                    |  |
| subjects affected / exposed   | 5 / 246 (2.03%)    | 6 / 255 (2.35%)    |  |
| occurrences causally related to treatment / all                     | 0 / 5              | 0 / 8              |  |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 0              |  |
| Acute myeloid leukaemia   |                    |                    |  |
| subjects affected / exposed   | 6 / 246 (2.44%)    | 2 / 255 (0.78%)    |  |
| occurrences causally related to treatment / all                     | 0 / 6              | 0 / 2              |  |
| deaths causally related to treatment / all                          | 0 / 2              | 0 / 1              |  |
| Acute lymphocytic leukaemia   |                    |                    |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 0 / 246 (0.00%)  | 1 / 255 (0.39%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Basal cell carcinoma                            |                  |                  |  |
| subjects affected / exposed                     | 2 / 246 (0.81%)  | 0 / 255 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Acute myeloid leukaemia recurrent               |                  |                  |  |
| subjects affected / exposed                     | 17 / 246 (6.91%) | 18 / 255 (7.06%) |  |
| occurrences causally related to treatment / all | 2 / 22           | 0 / 21           |  |
| deaths causally related to treatment / all      | 1 / 10           | 0 / 8            |  |
| Central nervous system lymphoma                 |                  |                  |  |
| subjects affected / exposed                     | 0 / 246 (0.00%)  | 1 / 255 (0.39%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Adult T-cell lymphoma/leukaemia recurrent       |                  |                  |  |
| subjects affected / exposed                     | 1 / 246 (0.41%)  | 0 / 255 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chronic lymphocytic leukaemia recurrent         |                  |                  |  |
| subjects affected / exposed                     | 1 / 246 (0.41%)  | 0 / 255 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chloroma  |                  |                  |  |
| subjects affected / exposed                     | 1 / 246 (0.41%)  | 1 / 255 (0.39%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Chronic lymphocytic leukaemia                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 246 (0.00%)  | 1 / 255 (0.39%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Chronic myelomonocytic leukaemia                |                  |                  |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diffuse large B-cell lymphoma                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| 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                     | 2 / 246 (0.81%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Leukaemia recurrent                             |                 |                 |  |
| subjects affected / exposed                     | 3 / 246 (1.22%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Hodgkin's disease                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Kaposi's sarcoma                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic cancer metastatic                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Lymphoma  |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Malignant melanoma                              |                 |                 |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                      | 2 / 246 (0.81%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all  | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all       | 0 / 0           | 0 / 0           |  |
| Leukaemic infiltration brain                     |                 |                 |  |
| subjects affected / exposed                      | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all  | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all       | 0 / 0           | 0 / 0           |  |
| Monoclonal gammopathy                            |                 |                 |  |
| subjects affected / exposed                      | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all  | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all       | 0 / 0           | 0 / 0           |  |
| Malignant neoplasm progression                   |                 |                 |  |
| subjects affected / exposed                      | 2 / 246 (0.81%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all  | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all       | 0 / 2           | 0 / 1           |  |
| Mycosis fungoides recurrent                      |                 |                 |  |
| subjects affected / exposed                      | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all  | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all       | 0 / 0           | 0 / 0           |  |
| Myelodysplastic syndrome                         |                 |                 |  |
| subjects affected / exposed                      | 5 / 246 (2.03%) | 3 / 255 (1.18%) |  |
| occurrences causally related to treatment / all  | 1 / 5           | 0 / 3           |  |
| deaths causally related to treatment / all       | 0 / 0           | 0 / 1           |  |
| Peripheral T-cell lymphoma unspecified recurrent |                 |                 |  |
| subjects affected / exposed                      | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all  | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all       | 0 / 0           | 0 / 0           |  |
| Non-Hodgkin's lymphoma recurrent                 |                 |                 |  |
| subjects affected / exposed                      | 0 / 246 (0.00%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all  | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all       | 0 / 0           | 0 / 0           |  |
| Myelofibrosis                                    |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Small cell lung cancer                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| 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                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Squamous cell carcinoma of skin                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Post transplant lymphoproliferative disorder    |                 |                 |  |
| subjects affected / exposed                     | 2 / 246 (0.81%) | 3 / 255 (1.18%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| T-cell lymphoma                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| T-cell lymphoma recurrent                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| T-cell type acute leukaemia                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular disorders                              |                 |                 |  |
| Deep vein thrombosis                            |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 246 (0.00%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematoma                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypotension                                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 246 (0.81%) | 3 / 255 (1.18%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Microangiopathy                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thrombophlebitis                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Orthostatic hypotension                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (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                     | 1 / 246 (0.41%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| Venous thrombosis                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Surgical and medical procedures                 |                 |                 |  |
| Appendicectomy                                  |                 |                 |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                          | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Central venous catheter removal                      |                 |                 |  |
| subjects affected / exposed                          | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Colectomy  |                 |                 |  |
| subjects affected / exposed                          | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Drug therapy   |                 |                 |  |
| subjects affected / exposed                          | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Donor leukocyte infusion                             |                 |                 |  |
| subjects affected / exposed                          | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Stem cell transplant                                 |                 |                 |  |
| subjects affected / exposed                          | 2 / 246 (0.81%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all      | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Transurethral prostatectomy                          |                 |                 |  |
| subjects affected / exposed                          | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Asthenia   |                 |                 |  |
| subjects affected / exposed                          | 4 / 246 (1.63%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all      | 1 / 4           | 0 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Chest pain   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chills  |                 |                 |  |
| subjects affected / exposed                     | 3 / 246 (1.22%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Drug resistance                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fatigue   |                 |                 |  |
| subjects affected / exposed                     | 2 / 246 (0.81%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| General physical health deterioration           |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infusion site extravasation                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Malaise   |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mucosal inflammation                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Non-cardiac chest pain                          |                 |                 |  |

|   |                   |                  |  |
|---|-------------------|------------------|--|
| subjects affected / exposed                     | 1 / 246 (0.41%)   | 1 / 255 (0.39%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Multi-organ failure                             |                   |                  |  |
| subjects affected / exposed                     | 6 / 246 (2.44%)   | 2 / 255 (0.78%)  |  |
| occurrences causally related to treatment / all | 0 / 6             | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 5             | 0 / 2            |  |
| Oedema due to cardiac disease                   |                   |                  |  |
| subjects affected / exposed                     | 1 / 246 (0.41%)   | 0 / 255 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Sudden death                                    |                   |                  |  |
| subjects affected / exposed                     | 1 / 246 (0.41%)   | 1 / 255 (0.39%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 1            |  |
| Serositis                                       |                   |                  |  |
| subjects affected / exposed                     | 1 / 246 (0.41%)   | 0 / 255 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Pyrexia   |                   |                  |  |
| subjects affected / exposed                     | 26 / 246 (10.57%) | 23 / 255 (9.02%) |  |
| occurrences causally related to treatment / all | 2 / 27            | 0 / 29           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Systemic inflammatory response syndrome         |                   |                  |  |
| subjects affected / exposed                     | 2 / 246 (0.81%)   | 0 / 255 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Immune system disorders                         |                   |                  |  |
| Acute graft versus host disease                 |                   |                  |  |
| subjects affected / exposed                     | 7 / 246 (2.85%)   | 9 / 255 (3.53%)  |  |
| occurrences causally related to treatment / all | 0 / 7             | 0 / 10           |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0            |  |
| Acute graft versus host disease in intestine    |                   |                  |  |

|   |                    |                    |  |
|---|--------------------|--------------------|--|
| subjects affected / exposed                     | 76 / 246 (30.89%)  | 76 / 255 (29.80%)  |  |
| occurrences causally related to treatment / all | 1 / 123            | 0 / 120            |  |
| deaths causally related to treatment / all      | 1 / 3              | 0 / 8              |  |
| Acute graft versus host disease in liver        |                    |                    |  |
| subjects affected / exposed                     | 18 / 246 (7.32%)   | 24 / 255 (9.41%)   |  |
| occurrences causally related to treatment / all | 1 / 23             | 0 / 30             |  |
| deaths causally related to treatment / all      | 1 / 2              | 0 / 3              |  |
| Acute graft versus host disease in skin         |                    |                    |  |
| subjects affected / exposed                     | 118 / 246 (47.97%) | 122 / 255 (47.84%) |  |
| occurrences causally related to treatment / all | 3 / 165            | 1 / 171            |  |
| deaths causally related to treatment / all      | 0 / 0              | 0 / 3              |  |
| Alloimmunisation                                |                    |                    |  |
| subjects affected / exposed                     | 0 / 246 (0.00%)    | 1 / 255 (0.39%)    |  |
| occurrences causally related to treatment / all | 0 / 0              | 0 / 1              |  |
| deaths causally related to treatment / all      | 0 / 0              | 0 / 0              |  |
| Chronic graft versus host disease               |                    |                    |  |
| subjects affected / exposed                     | 2 / 246 (0.81%)    | 4 / 255 (1.57%)    |  |
| occurrences causally related to treatment / all | 0 / 2              | 0 / 5              |  |
| deaths causally related to treatment / all      | 0 / 0              | 0 / 0              |  |
| Chronic graft versus host disease in intestine  |                    |                    |  |
| subjects affected / exposed                     | 3 / 246 (1.22%)    | 6 / 255 (2.35%)    |  |
| occurrences causally related to treatment / all | 0 / 3              | 0 / 7              |  |
| deaths causally related to treatment / all      | 0 / 0              | 0 / 1              |  |
| Chronic graft versus host disease in skin       |                    |                    |  |
| subjects affected / exposed                     | 1 / 246 (0.41%)    | 5 / 255 (1.96%)    |  |
| occurrences causally related to treatment / all | 0 / 1              | 0 / 5              |  |
| deaths causally related to treatment / all      | 0 / 0              | 0 / 0              |  |
| Chronic graft versus host disease in liver      |                    |                    |  |
| subjects affected / exposed                     | 3 / 246 (1.22%)    | 7 / 255 (2.75%)    |  |
| occurrences causally related to treatment / all | 0 / 3              | 0 / 7              |  |
| deaths causally related to treatment / all      | 0 / 0              | 0 / 2              |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Acute pulmonary oedema                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute respiratory distress syndrome             |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 6 / 255 (2.35%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 5           |  |
| Acute respiratory failure                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 246 (0.81%) | 4 / 255 (1.57%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 4           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| Atelectasis                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dyspnoea  |                 |                 |  |
| subjects affected / exposed                     | 3 / 246 (1.22%) | 4 / 255 (1.57%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cough   |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dyspnoea exertional                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Epistaxis                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Haemoptysis                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoxia   |                 |                 |  |
| subjects affected / exposed                     | 3 / 246 (1.22%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Idiopathic pneumonia syndrome                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Interstitial lung disease                       |                 |                 |  |
| subjects affected / exposed                     | 3 / 246 (1.22%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Mediastinal mass                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Obliterative bronchiolitis                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Obstructive airways disorder                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pleural effusion                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Organising pneumonia                            |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 246 (0.81%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| Pneumonitis                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 7 / 255 (2.75%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 7           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary alveolar haemorrhage                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| Pulmonary embolism                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary haemorrhage                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| Pulmonary oedema                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Pulmonary thrombosis                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory arrest                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory distress                            |                 |                 |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 1 / 246 (0.41%) | 2 / 255 (0.78%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Wheezing  |                 |                  |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Respiratory failure                             |                 |                  |  |
| subjects affected / exposed                     | 8 / 246 (3.25%) | 11 / 255 (4.31%) |  |
| occurrences causally related to treatment / all | 0 / 8           | 0 / 13           |  |
| deaths causally related to treatment / all      | 0 / 5           | 0 / 5            |  |
| Psychiatric disorders                           |                 |                  |  |
| Confusional state                               |                 |                  |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 2 / 255 (0.78%)  |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Disorientation                                  |                 |                  |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Delirium  |                 |                  |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 1 / 255 (0.39%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Mania   |                 |                  |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Mental disorder                                 |                 |                  |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 1 / 255 (0.39%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Mental status changes                           |                 |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 3 / 246 (1.22%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Suicidal ideation                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Blood bilirubin increased                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Liver function test abnormal                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Immunosuppressant drug level increased          |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Computerised tomogram thorax abnormal           |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Weight decreased                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Transaminases increased                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Platelet count decreased                        |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 246 (0.41%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 3 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |
| Blood stem cell transplant failure              |                 |                 |  |
| subjects affected / exposed                     | 3 / 246 (1.22%) | 4 / 255 (1.57%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 1 / 4           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 2           |  |
| Drug dose omission                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Facial bones fracture                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Muscle strain                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fall  |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal compression fracture                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Road traffic accident                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Spinal fracture                                 |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Transplant failure                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 3 / 255 (1.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Transfusion microchimerism                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (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                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Acute myocardial infarction                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Angina pectoris                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 4 / 246 (1.63%) | 3 / 255 (1.18%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Cardiac failure                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arrhythmia                                      |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure acute                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac tamponade                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac failure congestive                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardio-respiratory arrest                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Pericardial effusion                            |                 |                 |  |
| subjects affected / exposed                     | 2 / 246 (0.81%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiogenic shock                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Pericarditis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulseless electrical activity                   |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Supraventricular tachycardia                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Acute polyneuropathy                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Amnesia   |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Brain oedema                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Central nervous system lesion                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (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                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Convulsion                                      |                 |                 |  |
| subjects affected / exposed                     | 3 / 246 (1.22%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coma  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dizziness                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 246 (0.81%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Encephalitis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Encephalopathy                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 246 (0.81%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Headache  |                 |                 |  |
| subjects affected / exposed                     | 2 / 246 (0.81%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Facial paresis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Memory impairment                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Migraine  |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neurological decompensation                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 246 (0.41%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Paraplegia                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Syncope   |                 |                 |  |
| subjects affected / exposed                     | 2 / 246 (0.81%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thalamus haemorrhage                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Transient ischaemic attack                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 246 (0.81%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| VIIth nerve paralysis                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood and lymphatic system disorders            |                 |                 |  |
| Agranulocytosis                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 3 / 255 (1.18%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Anaemia   |                 |                 |  |
| subjects affected / exposed                     | 3 / 246 (1.22%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 1 / 4           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coagulopathy                                    |                 |                 |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 2 / 246 (0.81%)  | 0 / 255 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Aplasia pure red cell                           |                  |                  |  |
| subjects affected / exposed                     | 1 / 246 (0.41%)  | 1 / 255 (0.39%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Eosinophilia                                    |                  |                  |  |
| subjects affected / exposed                     | 1 / 246 (0.41%)  | 0 / 255 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Bone marrow failure                             |                  |                  |  |
| subjects affected / exposed                     | 3 / 246 (1.22%)  | 1 / 255 (0.39%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Febrile bone marrow aplasia                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 246 (0.00%)  | 1 / 255 (0.39%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Febrile neutropenia                             |                  |                  |  |
| subjects affected / exposed                     | 11 / 246 (4.47%) | 11 / 255 (4.31%) |  |
| occurrences causally related to treatment / all | 0 / 14           | 0 / 13           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Haemolytic anaemia                              |                  |                  |  |
| subjects affected / exposed                     | 3 / 246 (1.22%)  | 2 / 255 (0.78%)  |  |
| occurrences causally related to treatment / all | 1 / 3            | 1 / 2            |  |
| deaths causally related to treatment / all      | 1 / 1            | 0 / 0            |  |
| Haemolytic uraemic syndrome                     |                  |                  |  |
| subjects affected / exposed                     | 0 / 246 (0.00%)  | 1 / 255 (0.39%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Neutropenia                                     |                  |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancytopenia                                    |                 |                 |  |
| subjects affected / exposed                     | 5 / 246 (2.03%) | 5 / 255 (1.96%) |  |
| occurrences causally related to treatment / all | 0 / 6           | 1 / 6           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| Thrombocytopenia                                |                 |                 |  |
| subjects affected / exposed                     | 3 / 246 (1.22%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thrombotic microangiopathy                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Ear and labyrinth disorders                     |                 |                 |  |
| Aural polyp                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Deafness neurosensory                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Eye disorders                                   |                 |                 |  |
| Mydriasis                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Abdominal discomfort                            |                 |                 |  |
| subjects affected / exposed                     | 2 / 246 (0.81%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| Abdominal pain                                  |                  |                  |  |
| subjects affected / exposed                     | 2 / 246 (0.81%)  | 2 / 255 (0.78%)  |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Abdominal pain lower                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 246 (0.00%)  | 1 / 255 (0.39%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Anal fissure                                    |                  |                  |  |
| subjects affected / exposed                     | 0 / 246 (0.00%)  | 1 / 255 (0.39%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Ascites   |                  |                  |  |
| subjects affected / exposed                     | 0 / 246 (0.00%)  | 1 / 255 (0.39%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Colitis   |                  |                  |  |
| subjects affected / exposed                     | 1 / 246 (0.41%)  | 0 / 255 (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                     | 0 / 246 (0.00%)  | 1 / 255 (0.39%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Diarrhoea                                       |                  |                  |  |
| subjects affected / exposed                     | 10 / 246 (4.07%) | 11 / 255 (4.31%) |  |
| occurrences causally related to treatment / all | 1 / 13           | 0 / 11           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Enterocolitis                                   |                  |                  |  |
| subjects affected / exposed                     | 0 / 246 (0.00%)  | 1 / 255 (0.39%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Enteritis                                       |                  |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastritis                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrooesophagitis                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (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                     | 2 / 246 (0.81%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Gastrointestinal toxicity                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematochezia                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Impaired gastric emptying                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intra-abdominal haemorrhage                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Large intestinal haemorrhage                    |                 |                 |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 0 / 246 (0.00%)  | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Nausea  |                  |                 |  |
| subjects affected / exposed                     | 10 / 246 (4.07%) | 8 / 255 (3.14%) |  |
| occurrences causally related to treatment / all | 1 / 10           | 0 / 8           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Megacolon                                       |                  |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%)  | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1           |  |
| Oesophagitis                                    |                  |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%)  | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Oral pain                                       |                  |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%)  | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pancreatitis                                    |                  |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%)  | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pancreatitis acute                              |                  |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%)  | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Pneumatosis intestinalis                        |                  |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%)  | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Small intestinal perforation                    |                  |                 |  |



|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 0 / 246 (0.00%)  | 1 / 255 (0.39%) |  |
| 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                     | 2 / 246 (0.81%)  | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Proctalgia                                      |                  |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%)  | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Vomiting  |                  |                 |  |
| subjects affected / exposed                     | 11 / 246 (4.47%) | 7 / 255 (2.75%) |  |
| occurrences causally related to treatment / all | 0 / 12           | 0 / 7           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Upper gastrointestinal haemorrhage              |                  |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%)  | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hepatobiliary disorders                         |                  |                 |  |
| Cholecystitis                                   |                  |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%)  | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Acute hepatic failure                           |                  |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%)  | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0           |  |
| Cholecystitis acute                             |                  |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%)  | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Hepatic vein occlusion                          |                  |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperbilirubinaemia                             |                 |                 |  |
| subjects affected / exposed                     | 2 / 246 (0.81%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Venoocclusive liver disease                     |                 |                 |  |
| subjects affected / exposed                     | 5 / 246 (2.03%) | 4 / 255 (1.57%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| Skin and subcutaneous tissue disorders          |                 |                 |  |
| Diabetic foot                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pain of skin                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rash  |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 1 / 255 (0.39%) |  |
| 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                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Stasis dermatitis                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin lesion                                     |                 |                 |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 1 / 246 (0.41%)   | 0 / 255 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Toxic epidermal necrolysis                      |                   |                   |  |
| subjects affected / exposed                     | 1 / 246 (0.41%)   | 1 / 255 (0.39%)   |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 1             |  |
| Urticaria                                       |                   |                   |  |
| subjects affected / exposed                     | 1 / 246 (0.41%)   | 0 / 255 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Renal and urinary disorders                     |                   |                   |  |
| Haematuria                                      |                   |                   |  |
| subjects affected / exposed                     | 1 / 246 (0.41%)   | 0 / 255 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Renal colic                                     |                   |                   |  |
| subjects affected / exposed                     | 1 / 246 (0.41%)   | 0 / 255 (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                     | 3 / 246 (1.22%)   | 5 / 255 (1.96%)   |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 6             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 2             |  |
| Renal failure acute                             |                   |                   |  |
| subjects affected / exposed                     | 28 / 246 (11.38%) | 41 / 255 (16.08%) |  |
| occurrences causally related to treatment / all | 0 / 38            | 0 / 46            |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Renal injury                                    |                   |                   |  |
| subjects affected / exposed                     | 1 / 246 (0.41%)   | 0 / 255 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Renal impairment                                |                   |                   |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 246 (0.00%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal failure chronic                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Renal tubular necrosis                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract obstruction                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Endocrine disorders                             |                 |                 |  |
| Inappropriate antidiuretic hormone secretion    |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| 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 |                 |                 |  |
| Chondrocalcinosis pyrophosphate                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Back pain                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arthralgia                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Myopathy  |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rhabdomyolysis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Polyarthritis                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intervertebral disc protrusion                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Abdominal abscess                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abscess intestinal                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Acinetobacter bacteraemia                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 246 (0.81%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Adenovirus infection                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Anorectal cellulitis                            |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Appendicitis                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Aspergillosis                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Atypical mycobacterial infection                |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atypical pneumonia                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bacteraemia                                     |                 |                 |  |
| subjects affected / exposed                     | 4 / 246 (1.63%) | 4 / 255 (1.57%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 1 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| BK virus infection                              |                 |                 |  |
| subjects affected / exposed                     | 2 / 246 (0.81%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bacterial infection                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Brain abscess                                   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Bacterial sepsis                                |                 |                 |  |
| subjects affected / exposed                     | 3 / 246 (1.22%) | 3 / 255 (1.18%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Bronchitis                                      |                 |                 |  |
| subjects affected / exposed                     | 2 / 246 (0.81%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchopneumonia                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Campylobacter gastroenteritis                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bronchopulmonary aspergillosis                  |                 |                 |  |
| subjects affected / exposed                     | 4 / 246 (1.63%) | 3 / 255 (1.18%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 2           |  |
| Catheter site infection                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (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                     | 3 / 246 (1.22%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebral aspergillosis                          |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Citrobacter sepsis                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Clostridium difficile colitis                   |                 |                 |  |
| subjects affected / exposed                     | 2 / 246 (0.81%) | 5 / 255 (1.96%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Clostridium difficile infection                 |                 |                 |  |
| subjects affected / exposed                     | 3 / 246 (1.22%) | 4 / 255 (1.57%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Corona virus infection                          |                 |                 |  |
| subjects affected / exposed                     | 2 / 246 (0.81%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cystitis  |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cytomegalovirus gastritis                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 246 (0.81%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cytomegalovirus colitis                         |                 |                 |  |
| subjects affected / exposed                     | 3 / 246 (1.22%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Cystitis bacterial                              |                 |                 |  |



|   |                  |                 |  |
|---|------------------|-----------------|--|
| subjects affected / exposed                     | 1 / 246 (0.41%)  | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Cytomegalovirus gastroenteritis                 |                  |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%)  | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Cytomegalovirus infection                       |                  |                 |  |
| subjects affected / exposed                     | 10 / 246 (4.07%) | 6 / 255 (2.35%) |  |
| occurrences causally related to treatment / all | 0 / 10           | 1 / 6           |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 0           |  |
| Cytomegalovirus viraemia                        |                  |                 |  |
| subjects affected / exposed                     | 11 / 246 (4.47%) | 9 / 255 (3.53%) |  |
| occurrences causally related to treatment / all | 2 / 13           | 1 / 11          |  |
| deaths causally related to treatment / all      | 0 / 2            | 0 / 2           |  |
| Device related infection                        |                  |                 |  |
| subjects affected / exposed                     | 2 / 246 (0.81%)  | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 2            | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Diverticulitis                                  |                  |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%)  | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Diarrhoea infectious                            |                  |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%)  | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Device related sepsis                           |                  |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%)  | 3 / 255 (1.18%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Encephalitis cytomegalovirus                    |                  |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Encephalitis herpes                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Encephalitis viral                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Enterococcal bacteraemia                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enterococcal sepsis                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enterocolitis bacterial                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Epstein-Barr viraemia                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enterocolitis infectious                        |                 |                 |  |
| subjects affected / exposed                     | 2 / 246 (0.81%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Escherichia bacteraemia                         |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Epstein-Barr virus infection                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Escherichia sepsis                              |                 |                 |  |
| subjects affected / exposed                     | 3 / 246 (1.22%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Escherichia urinary tract infection             |                 |                 |  |
| subjects affected / exposed                     | 2 / 246 (0.81%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gangrene  |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis adenovirus                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Genital herpes                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic candidiasis                             |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Herpes simplex                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Herpes zoster                                   |                 |                 |  |
| subjects affected / exposed                     | 4 / 246 (1.63%) | 5 / 255 (1.96%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 7           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Herpes zoster ophthalmic                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Human polyomavirus infection                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Human herpesvirus 6 infection                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infection                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 246 (0.81%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infected skin ulcer                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Influenza                                       |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 3 / 246 (1.22%) | 3 / 255 (1.18%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Klebsiella bacteraemia                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Localised infection                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lobar pneumonia                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Klebsiella sepsis                               |                 |                 |  |
| subjects affected / exposed                     | 2 / 246 (0.81%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Lower respiratory tract infection bacterial     |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (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                     | 4 / 246 (1.63%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Meningitis aseptic                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oesophageal candidiasis                         |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oral candidiasis                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neutropenic sepsis                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oral herpes                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peritonitis                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pharyngitis                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumocystis jiroveci pneumonia                 |                 |                 |  |
| subjects affected / exposed                     | 2 / 246 (0.81%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia bacterial                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Pneumonia adenoviral                            |                 |                 |  |

|   |                  |                  |  |
|---|------------------|------------------|--|
| subjects affected / exposed                     | 1 / 246 (0.41%)  | 1 / 255 (0.39%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Pneumonia                                       |                  |                  |  |
| subjects affected / exposed                     | 19 / 246 (7.72%) | 15 / 255 (5.88%) |  |
| occurrences causally related to treatment / all | 0 / 20           | 1 / 18           |  |
| deaths causally related to treatment / all      | 0 / 5            | 0 / 6            |  |
| Pneumonia fungal                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 246 (0.41%)  | 2 / 255 (0.78%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Pneumonia escherichia                           |                  |                  |  |
| subjects affected / exposed                     | 0 / 246 (0.00%)  | 1 / 255 (0.39%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pneumonia herpes viral                          |                  |                  |  |
| subjects affected / exposed                     | 0 / 246 (0.00%)  | 1 / 255 (0.39%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Pneumonia cytomegaloviral                       |                  |                  |  |
| subjects affected / exposed                     | 3 / 246 (1.22%)  | 1 / 255 (0.39%)  |  |
| occurrences causally related to treatment / all | 0 / 3            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Pneumonia legionella                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 246 (0.00%)  | 2 / 255 (0.78%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pneumonia klebsiella                            |                  |                  |  |
| subjects affected / exposed                     | 0 / 246 (0.00%)  | 1 / 255 (0.39%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Pneumonia influenzal                            |                  |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 246 (0.41%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia respiratory syncytial viral           |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia staphylococcal                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Pneumonia viral                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pneumonia streptococcal                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pseudomonal bacteraemia                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Postoperative wound infection                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary mycosis                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (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                     | 14 / 246 (5.69%) | 20 / 255 (7.84%) |  |
| occurrences causally related to treatment / all | 0 / 14           | 1 / 23           |  |
| deaths causally related to treatment / all      | 0 / 3            | 0 / 8            |  |
| Respiratory tract infection                     |                  |                  |  |
| subjects affected / exposed                     | 4 / 246 (1.63%)  | 3 / 255 (1.18%)  |  |
| occurrences causally related to treatment / all | 0 / 5            | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Respiratory syncytial virus infection           |                  |                  |  |
| subjects affected / exposed                     | 1 / 246 (0.41%)  | 2 / 255 (0.78%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 1            |  |
| Septic shock                                    |                  |                  |  |
| subjects affected / exposed                     | 10 / 246 (4.07%) | 9 / 255 (3.53%)  |  |
| occurrences causally related to treatment / all | 0 / 10           | 0 / 10           |  |
| deaths causally related to treatment / all      | 0 / 7            | 0 / 3            |  |
| Sialoadenitis                                   |                  |                  |  |
| subjects affected / exposed                     | 1 / 246 (0.41%)  | 0 / 255 (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 / 246 (0.41%)  | 3 / 255 (1.18%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Sinusitis fungal                                |                  |                  |  |
| subjects affected / exposed                     | 1 / 246 (0.41%)  | 0 / 255 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 1            | 0 / 0            |  |
| Skin infection                                  |                  |                  |  |
| subjects affected / exposed                     | 0 / 246 (0.00%)  | 1 / 255 (0.39%)  |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0            |  |
| Staphylococcal bacteraemia                      |                  |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 5 / 246 (2.03%) | 4 / 255 (1.57%) |  |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Staphylococcal sepsis                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Streptococcal bacteraemia                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Systemic mycosis                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subcutaneous abscess                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Streptococcal sepsis                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tubo-ovarian abscess                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 4 / 246 (1.63%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 246 (0.81%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection bacterial               |                 |                 |  |
| subjects affected / exposed                     | 3 / 246 (1.22%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection enterococcal            |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection fungal                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Viral infection                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Viral haemorrhagic cystitis                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 246 (0.81%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Cachexia  |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Decreased appetite                              |                 |                 |  |
| subjects affected / exposed                     | 2 / 246 (0.81%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dehydration                                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 4 / 246 (1.63%) | 4 / 255 (1.57%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetes mellitus                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetes mellitus inadequate control            |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Failure to thrive                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Fluid overload                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypercalcaemia                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 246 (0.00%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperglycaemia                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 246 (0.81%) | 2 / 255 (0.78%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoalbuminaemia                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperkalaemia                                   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 246 (0.81%) | 1 / 255 (0.39%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Hypocalcaemia</b>                            |                 |                 |  |
| subjects affected / exposed                     | 2 / 246 (0.81%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Hyponatraemia</b>                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Malnutrition</b>                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Tumour lysis syndrome</b>                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 246 (0.41%) | 0 / 255 (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>                            | ASP0113 5mg        | Placebo            |  |
|--|--------------------|--------------------|--|
| <b>Total subjects affected by non-serious adverse events</b> |                    |                    |  |
| subjects affected / exposed                                  | 244 / 246 (99.19%) | 254 / 255 (99.61%) |  |
| <b>Vascular disorders</b>                                    |                    |                    |  |
| <b>Hypertension</b>  |                    |                    |  |
| subjects affected / exposed                                  | 66 / 246 (26.83%)  | 83 / 255 (32.55%)  |  |
| occurrences (all)  | 78                 | 96                 |  |
| <b>Hypotension</b>   |                    |                    |  |
| subjects affected / exposed                                  | 39 / 246 (15.85%)  | 36 / 255 (14.12%)  |  |
| occurrences (all)  | 50                 | 37                 |  |
| <b>General disorders and administration site conditions</b>  |                    |                    |  |

|                             |                    |                    |
|-----------------------------|--------------------|--------------------|
| Asthenia                    |                    |                    |
| subjects affected / exposed | 30 / 246 (12.20%)  | 34 / 255 (13.33%)  |
| occurrences (all)           | 39                 | 43                 |
| Injection site erythema     |                    |                    |
| subjects affected / exposed | 49 / 246 (19.92%)  | 5 / 255 (1.96%)    |
| occurrences (all)           | 72                 | 5                  |
| Fatigue                     |                    |                    |
| subjects affected / exposed | 58 / 246 (23.58%)  | 69 / 255 (27.06%)  |
| occurrences (all)           | 65                 | 80                 |
| Chills                      |                    |                    |
| subjects affected / exposed | 36 / 246 (14.63%)  | 44 / 255 (17.25%)  |
| occurrences (all)           | 46                 | 59                 |
| Catheter site pain          |                    |                    |
| subjects affected / exposed | 22 / 246 (8.94%)   | 21 / 255 (8.24%)   |
| occurrences (all)           | 29                 | 23                 |
| Injection site induration   |                    |                    |
| subjects affected / exposed | 38 / 246 (15.45%)  | 3 / 255 (1.18%)    |
| occurrences (all)           | 57                 | 3                  |
| Mucosal inflammation        |                    |                    |
| subjects affected / exposed | 75 / 246 (30.49%)  | 101 / 255 (39.61%) |
| occurrences (all)           | 94                 | 147                |
| Malaise                     |                    |                    |
| subjects affected / exposed | 15 / 246 (6.10%)   | 10 / 255 (3.92%)   |
| occurrences (all)           | 15                 | 11                 |
| Injection site swelling     |                    |                    |
| subjects affected / exposed | 24 / 246 (9.76%)   | 4 / 255 (1.57%)    |
| occurrences (all)           | 36                 | 4                  |
| Injection site pain         |                    |                    |
| subjects affected / exposed | 193 / 246 (78.46%) | 47 / 255 (18.43%)  |
| occurrences (all)           | 1053               | 83                 |
| Oedema                      |                    |                    |
| subjects affected / exposed | 35 / 246 (14.23%)  | 21 / 255 (8.24%)   |
| occurrences (all)           | 39                 | 24                 |
| Oedema peripheral           |                    |                    |
| subjects affected / exposed | 66 / 246 (26.83%)  | 69 / 255 (27.06%)  |
| occurrences (all)           | 88                 | 95                 |

|   |                    |                    |  |
|---|--------------------|--------------------|--|
| Pain  |                    |                    |  |
| subjects affected / exposed                     | 27 / 246 (10.98%)  | 32 / 255 (12.55%)  |  |
| occurrences (all)                               | 34                 | 34                 |  |
| Pyrexia   |                    |                    |  |
| subjects affected / exposed                     | 123 / 246 (50.00%) | 128 / 255 (50.20%) |  |
| occurrences (all)                               | 180                | 195                |  |
| Immune system disorders                         |                    |                    |  |
| Chronic graft versus host disease               |                    |                    |  |
| subjects affected / exposed                     | 62 / 246 (25.20%)  | 60 / 255 (23.53%)  |  |
| occurrences (all)                               | 110                | 109                |  |
| Engraftment syndrome                            |                    |                    |  |
| subjects affected / exposed                     | 13 / 246 (5.28%)   | 9 / 255 (3.53%)    |  |
| occurrences (all)                               | 15                 | 9                  |  |
| Chronic graft versus host disease in skin       |                    |                    |  |
| subjects affected / exposed                     | 37 / 246 (15.04%)  | 46 / 255 (18.04%)  |  |
| occurrences (all)                               | 40                 | 51                 |  |
| Chronic graft versus host disease in liver      |                    |                    |  |
| subjects affected / exposed                     | 30 / 246 (12.20%)  | 35 / 255 (13.73%)  |  |
| occurrences (all)                               | 43                 | 45                 |  |
| Chronic graft versus host disease in intestine  |                    |                    |  |
| subjects affected / exposed                     | 20 / 246 (8.13%)   | 21 / 255 (8.24%)   |  |
| occurrences (all)                               | 22                 | 28                 |  |
| Hypogammaglobulinaemia                          |                    |                    |  |
| subjects affected / exposed                     | 20 / 246 (8.13%)   | 19 / 255 (7.45%)   |  |
| occurrences (all)                               | 20                 | 20                 |  |
| Respiratory, thoracic and mediastinal disorders |                    |                    |  |
| Dyspnoea  |                    |                    |  |
| subjects affected / exposed                     | 40 / 246 (16.26%)  | 44 / 255 (17.25%)  |  |
| occurrences (all)                               | 50                 | 53                 |  |
| Cough   |                    |                    |  |
| subjects affected / exposed                     | 55 / 246 (22.36%)  | 60 / 255 (23.53%)  |  |
| occurrences (all)                               | 71                 | 71                 |  |
| Epistaxis                                       |                    |                    |  |

|                                      |                   |                   |  |
|--------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed          | 34 / 246 (13.82%) | 23 / 255 (9.02%)  |  |
| occurrences (all)                    | 37                | 28                |  |
| Hiccups                              |                   |                   |  |
| subjects affected / exposed          | 22 / 246 (8.94%)  | 20 / 255 (7.84%)  |  |
| occurrences (all)                    | 24                | 21                |  |
| Hypoxia                              |                   |                   |  |
| subjects affected / exposed          | 17 / 246 (6.91%)  | 10 / 255 (3.92%)  |  |
| occurrences (all)                    | 21                | 12                |  |
| Nasal congestion                     |                   |                   |  |
| subjects affected / exposed          | 8 / 246 (3.25%)   | 18 / 255 (7.06%)  |  |
| occurrences (all)                    | 8                 | 20                |  |
| Oropharyngeal pain                   |                   |                   |  |
| subjects affected / exposed          | 30 / 246 (12.20%) | 41 / 255 (16.08%) |  |
| occurrences (all)                    | 33                | 42                |  |
| Rhinorrhoea                          |                   |                   |  |
| subjects affected / exposed          | 18 / 246 (7.32%)  | 16 / 255 (6.27%)  |  |
| occurrences (all)                    | 19                | 17                |  |
| Psychiatric disorders                |                   |                   |  |
| Anxiety                              |                   |                   |  |
| subjects affected / exposed          | 40 / 246 (16.26%) | 44 / 255 (17.25%) |  |
| occurrences (all)                    | 42                | 53                |  |
| Depression                           |                   |                   |  |
| subjects affected / exposed          | 11 / 246 (4.47%)  | 18 / 255 (7.06%)  |  |
| occurrences (all)                    | 11                | 18                |  |
| Insomnia                             |                   |                   |  |
| subjects affected / exposed          | 72 / 246 (29.27%) | 76 / 255 (29.80%) |  |
| occurrences (all)                    | 86                | 85                |  |
| Investigations                       |                   |                   |  |
| Alanine aminotransferase increased   |                   |                   |  |
| subjects affected / exposed          | 33 / 246 (13.41%) | 31 / 255 (12.16%) |  |
| occurrences (all)                    | 66                | 47                |  |
| Aspartate aminotransferase increased |                   |                   |  |
| subjects affected / exposed          | 30 / 246 (12.20%) | 30 / 255 (11.76%) |  |
| occurrences (all)                    | 49                | 45                |  |
| Blood alkaline phosphatase increased |                   |                   |  |



|  |                   |                   |  |
|--|-------------------|-------------------|--|
| subjects affected / exposed                    | 18 / 246 (7.32%)  | 17 / 255 (6.67%)  |  |
| occurrences (all)                              | 23                | 24                |  |
| Blood bilirubin increased                      |                   |                   |  |
| subjects affected / exposed                    | 21 / 246 (8.54%)  | 23 / 255 (9.02%)  |  |
| occurrences (all)                              | 43                | 48                |  |
| Blood creatinine increased                     |                   |                   |  |
| subjects affected / exposed                    | 22 / 246 (8.94%)  | 29 / 255 (11.37%) |  |
| occurrences (all)                              | 27                | 42                |  |
| Platelet count decreased                       |                   |                   |  |
| subjects affected / exposed                    | 28 / 246 (11.38%) | 37 / 255 (14.51%) |  |
| occurrences (all)                              | 49                | 83                |  |
| Neutrophil count decreased                     |                   |                   |  |
| subjects affected / exposed                    | 28 / 246 (11.38%) | 33 / 255 (12.94%) |  |
| occurrences (all)                              | 62                | 70                |  |
| Gamma-glutamyltransferase increased            |                   |                   |  |
| subjects affected / exposed                    | 15 / 246 (6.10%)  | 13 / 255 (5.10%)  |  |
| occurrences (all)                              | 26                | 24                |  |
| Transaminases increased                        |                   |                   |  |
| subjects affected / exposed                    | 18 / 246 (7.32%)  | 10 / 255 (3.92%)  |  |
| occurrences (all)                              | 19                | 11                |  |
| Weight decreased                               |                   |                   |  |
| subjects affected / exposed                    | 12 / 246 (4.88%)  | 15 / 255 (5.88%)  |  |
| occurrences (all)                              | 15                | 15                |  |
| White blood cell count decreased               |                   |                   |  |
| subjects affected / exposed                    | 24 / 246 (9.76%)  | 23 / 255 (9.02%)  |  |
| occurrences (all)                              | 45                | 65                |  |
| Injury, poisoning and procedural complications |                   |                   |  |
| Fall   |                   |                   |  |
| subjects affected / exposed                    | 15 / 246 (6.10%)  | 10 / 255 (3.92%)  |  |
| occurrences (all)                              | 17                | 12                |  |
| Cardiac disorders                              |                   |                   |  |
| Tachycardia                                    |                   |                   |  |
| subjects affected / exposed                    | 22 / 246 (8.94%)  | 22 / 255 (8.63%)  |  |
| occurrences (all)                              | 28                | 24                |  |
| Nervous system disorders                       |                   |                   |  |

|                                      |                    |                    |  |
|--------------------------------------|--------------------|--------------------|--|
| Dizziness                            |                    |                    |  |
| subjects affected / exposed          | 33 / 246 (13.41%)  | 33 / 255 (12.94%)  |  |
| occurrences (all)                    | 44                 | 38                 |  |
| Neuropathy peripheral                |                    |                    |  |
| subjects affected / exposed          | 14 / 246 (5.69%)   | 17 / 255 (6.67%)   |  |
| occurrences (all)                    | 17                 | 17                 |  |
| Headache                             |                    |                    |  |
| subjects affected / exposed          | 103 / 246 (41.87%) | 103 / 255 (40.39%) |  |
| occurrences (all)                    | 150                | 153                |  |
| Dysgeusia                            |                    |                    |  |
| subjects affected / exposed          | 23 / 246 (9.35%)   | 22 / 255 (8.63%)   |  |
| occurrences (all)                    | 24                 | 22                 |  |
| Tremor                               |                    |                    |  |
| subjects affected / exposed          | 23 / 246 (9.35%)   | 46 / 255 (18.04%)  |  |
| occurrences (all)                    | 24                 | 49                 |  |
| Blood and lymphatic system disorders |                    |                    |  |
| Anaemia                              |                    |                    |  |
| subjects affected / exposed          | 66 / 246 (26.83%)  | 75 / 255 (29.41%)  |  |
| occurrences (all)                    | 146                | 160                |  |
| Febrile neutropenia                  |                    |                    |  |
| subjects affected / exposed          | 91 / 246 (36.99%)  | 92 / 255 (36.08%)  |  |
| occurrences (all)                    | 101                | 98                 |  |
| Neutropenia                          |                    |                    |  |
| subjects affected / exposed          | 65 / 246 (26.42%)  | 65 / 255 (25.49%)  |  |
| occurrences (all)                    | 99                 | 98                 |  |
| Leukopenia                           |                    |                    |  |
| subjects affected / exposed          | 20 / 246 (8.13%)   | 23 / 255 (9.02%)   |  |
| occurrences (all)                    | 51                 | 56                 |  |
| Pancytopenia                         |                    |                    |  |
| subjects affected / exposed          | 21 / 246 (8.54%)   | 18 / 255 (7.06%)   |  |
| occurrences (all)                    | 21                 | 19                 |  |
| Thrombocytopenia                     |                    |                    |  |
| subjects affected / exposed          | 49 / 246 (19.92%)  | 48 / 255 (18.82%)  |  |
| occurrences (all)                    | 131                | 111                |  |
| Eye disorders                        |                    |                    |  |

|                                  |                    |                    |  |
|----------------------------------|--------------------|--------------------|--|
| Conjunctivitis                   |                    |                    |  |
| subjects affected / exposed      | 12 / 246 (4.88%)   | 17 / 255 (6.67%)   |  |
| occurrences (all)                | 12                 | 18                 |  |
| Dry eye                          |                    |                    |  |
| subjects affected / exposed      | 42 / 246 (17.07%)  | 37 / 255 (14.51%)  |  |
| occurrences (all)                | 45                 | 39                 |  |
| Gastrointestinal disorders       |                    |                    |  |
| Abdominal discomfort             |                    |                    |  |
| subjects affected / exposed      | 13 / 246 (5.28%)   | 8 / 255 (3.14%)    |  |
| occurrences (all)                | 15                 | 11                 |  |
| Abdominal pain                   |                    |                    |  |
| subjects affected / exposed      | 62 / 246 (25.20%)  | 60 / 255 (23.53%)  |  |
| occurrences (all)                | 84                 | 83                 |  |
| Abdominal distension             |                    |                    |  |
| subjects affected / exposed      | 15 / 246 (6.10%)   | 22 / 255 (8.63%)   |  |
| occurrences (all)                | 18                 | 22                 |  |
| Abdominal pain upper             |                    |                    |  |
| subjects affected / exposed      | 26 / 246 (10.57%)  | 33 / 255 (12.94%)  |  |
| occurrences (all)                | 32                 | 37                 |  |
| Diarrhoea                        |                    |                    |  |
| subjects affected / exposed      | 166 / 246 (67.48%) | 167 / 255 (65.49%) |  |
| occurrences (all)                | 242                | 244                |  |
| Constipation                     |                    |                    |  |
| subjects affected / exposed      | 90 / 246 (36.59%)  | 103 / 255 (40.39%) |  |
| occurrences (all)                | 119                | 128                |  |
| Dry mouth                        |                    |                    |  |
| subjects affected / exposed      | 30 / 246 (12.20%)  | 25 / 255 (9.80%)   |  |
| occurrences (all)                | 35                 | 31                 |  |
| Dyspepsia                        |                    |                    |  |
| subjects affected / exposed      | 31 / 246 (12.60%)  | 25 / 255 (9.80%)   |  |
| occurrences (all)                | 35                 | 27                 |  |
| Gastrooesophageal reflux disease |                    |                    |  |
| subjects affected / exposed      | 24 / 246 (9.76%)   | 16 / 255 (6.27%)   |  |
| occurrences (all)                | 25                 | 17                 |  |
| Gastritis                        |                    |                    |  |

|  |                    |                    |  |
|--|--------------------|--------------------|--|
| subjects affected / exposed            | 19 / 246 (7.72%)   | 19 / 255 (7.45%)   |  |
| occurrences (all)                      | 20                 | 19                 |  |
| Haemorrhoids                           |                    |                    |  |
| subjects affected / exposed            | 27 / 246 (10.98%)  | 23 / 255 (9.02%)   |  |
| occurrences (all)                      | 28                 | 26                 |  |
| Nausea                                 |                    |                    |  |
| subjects affected / exposed            | 178 / 246 (72.36%) | 177 / 255 (69.41%) |  |
| occurrences (all)                      | 273                | 261                |  |
| Oral pain                              |                    |                    |  |
| subjects affected / exposed            | 19 / 246 (7.72%)   | 16 / 255 (6.27%)   |  |
| occurrences (all)                      | 20                 | 17                 |  |
| Proctalgia                             |                    |                    |  |
| subjects affected / exposed            | 20 / 246 (8.13%)   | 20 / 255 (7.84%)   |  |
| occurrences (all)                      | 23                 | 20                 |  |
| Stomatitis                             |                    |                    |  |
| subjects affected / exposed            | 79 / 246 (32.11%)  | 69 / 255 (27.06%)  |  |
| occurrences (all)                      | 105                | 96                 |  |
| Vomiting                               |                    |                    |  |
| subjects affected / exposed            | 125 / 246 (50.81%) | 122 / 255 (47.84%) |  |
| occurrences (all)                      | 195                | 178                |  |
| Hepatobiliary disorders                |                    |                    |  |
| Hyperbilirubinaemia                    |                    |                    |  |
| subjects affected / exposed            | 13 / 246 (5.28%)   | 16 / 255 (6.27%)   |  |
| occurrences (all)                      | 17                 | 23                 |  |
| Skin and subcutaneous tissue disorders |                    |                    |  |
| Drug eruption                          |                    |                    |  |
| subjects affected / exposed            | 29 / 246 (11.79%)  | 30 / 255 (11.76%)  |  |
| occurrences (all)                      | 31                 | 32                 |  |
| Dry skin                               |                    |                    |  |
| subjects affected / exposed            | 25 / 246 (10.16%)  | 20 / 255 (7.84%)   |  |
| occurrences (all)                      | 26                 | 20                 |  |
| Rash maculo-papular                    |                    |                    |  |
| subjects affected / exposed            | 12 / 246 (4.88%)   | 13 / 255 (5.10%)   |  |
| occurrences (all)                      | 15                 | 17                 |  |
| Erythema                               |                    |                    |  |

|   |                         |                         |  |
|---|-------------------------|-------------------------|--|
| subjects affected / exposed<br>occurrences (all)                  | 34 / 246 (13.82%)<br>50 | 28 / 255 (10.98%)<br>37 |  |
| Pruritus<br>subjects affected / exposed<br>occurrences (all)      | 59 / 246 (23.98%)<br>67 | 67 / 255 (26.27%)<br>85 |  |
| Rash<br>subjects affected / exposed<br>occurrences (all)          | 51 / 246 (20.73%)<br>67 | 52 / 255 (20.39%)<br>61 |  |
| Renal and urinary disorders                                       |                         |                         |  |
| Dysuria<br>subjects affected / exposed<br>occurrences (all)       | 20 / 246 (8.13%)<br>25  | 29 / 255 (11.37%)<br>33 |  |
| Haematuria<br>subjects affected / exposed<br>occurrences (all)    | 7 / 246 (2.85%)<br>8    | 15 / 255 (5.88%)<br>15  |  |
| Pollakiuria<br>subjects affected / exposed<br>occurrences (all)   | 8 / 246 (3.25%)<br>9    | 14 / 255 (5.49%)<br>16  |  |
| Renal failure<br>subjects affected / exposed<br>occurrences (all) | 17 / 246 (6.91%)<br>19  | 16 / 255 (6.27%)<br>17  |  |
| Musculoskeletal and connective tissue disorders                   |                         |                         |  |
| Arthralgia<br>subjects affected / exposed<br>occurrences (all)    | 30 / 246 (12.20%)<br>42 | 27 / 255 (10.59%)<br>30 |  |
| Muscle spasms<br>subjects affected / exposed<br>occurrences (all) | 14 / 246 (5.69%)<br>15  | 19 / 255 (7.45%)<br>25  |  |
| Bone pain<br>subjects affected / exposed<br>occurrences (all)     | 10 / 246 (4.07%)<br>12  | 13 / 255 (5.10%)<br>14  |  |
| Back pain<br>subjects affected / exposed<br>occurrences (all)     | 44 / 246 (17.89%)<br>52 | 39 / 255 (15.29%)<br>39 |  |
| Muscular weakness   |                         |                         |  |

|                                     |                   |                   |  |
|-------------------------------------|-------------------|-------------------|--|
| subjects affected / exposed         | 10 / 246 (4.07%)  | 14 / 255 (5.49%)  |  |
| occurrences (all)                   | 10                | 15                |  |
| Neck pain                           |                   |                   |  |
| subjects affected / exposed         | 16 / 246 (6.50%)  | 10 / 255 (3.92%)  |  |
| occurrences (all)                   | 18                | 10                |  |
| Myalgia                             |                   |                   |  |
| subjects affected / exposed         | 19 / 246 (7.72%)  | 19 / 255 (7.45%)  |  |
| occurrences (all)                   | 23                | 22                |  |
| Musculoskeletal pain                |                   |                   |  |
| subjects affected / exposed         | 19 / 246 (7.72%)  | 14 / 255 (5.49%)  |  |
| occurrences (all)                   | 21                | 14                |  |
| Pain in extremity                   |                   |                   |  |
| subjects affected / exposed         | 32 / 246 (13.01%) | 30 / 255 (11.76%) |  |
| occurrences (all)                   | 37                | 31                |  |
| Infections and infestations         |                   |                   |  |
| Clostridium difficile infection     |                   |                   |  |
| subjects affected / exposed         | 17 / 246 (6.91%)  | 16 / 255 (6.27%)  |  |
| occurrences (all)                   | 18                | 16                |  |
| BK virus infection                  |                   |                   |  |
| subjects affected / exposed         | 13 / 246 (5.28%)  | 13 / 255 (5.10%)  |  |
| occurrences (all)                   | 15                | 13                |  |
| Cytomegalovirus infection           |                   |                   |  |
| subjects affected / exposed         | 45 / 246 (18.29%) | 51 / 255 (20.00%) |  |
| occurrences (all)                   | 68                | 64                |  |
| Cytomegalovirus viraemia            |                   |                   |  |
| subjects affected / exposed         | 87 / 246 (35.37%) | 96 / 255 (37.65%) |  |
| occurrences (all)                   | 132               | 141               |  |
| Device related infection            |                   |                   |  |
| subjects affected / exposed         | 16 / 246 (6.50%)  | 16 / 255 (6.27%)  |  |
| occurrences (all)                   | 18                | 16                |  |
| Escherichia urinary tract infection |                   |                   |  |
| subjects affected / exposed         | 13 / 246 (5.28%)  | 11 / 255 (4.31%)  |  |
| occurrences (all)                   | 20                | 11                |  |
| Epstein-Barr virus infection        |                   |                   |  |
| subjects affected / exposed         | 15 / 246 (6.10%)  | 13 / 255 (5.10%)  |  |
| occurrences (all)                   | 16                | 15                |  |

|                                    |                   |                   |  |
|------------------------------------|-------------------|-------------------|--|
| Folliculitis                       |                   |                   |  |
| subjects affected / exposed        | 8 / 246 (3.25%)   | 14 / 255 (5.49%)  |  |
| occurrences (all)                  | 8                 | 18                |  |
| Oral candidiasis                   |                   |                   |  |
| subjects affected / exposed        | 17 / 246 (6.91%)  | 27 / 255 (10.59%) |  |
| occurrences (all)                  | 18                | 31                |  |
| Nasopharyngitis                    |                   |                   |  |
| subjects affected / exposed        | 15 / 246 (6.10%)  | 12 / 255 (4.71%)  |  |
| occurrences (all)                  | 15                | 14                |  |
| Oral herpes                        |                   |                   |  |
| subjects affected / exposed        | 8 / 246 (3.25%)   | 17 / 255 (6.67%)  |  |
| occurrences (all)                  | 13                | 18                |  |
| Pneumonia                          |                   |                   |  |
| subjects affected / exposed        | 13 / 246 (5.28%)  | 13 / 255 (5.10%)  |  |
| occurrences (all)                  | 13                | 13                |  |
| Upper respiratory tract infection  |                   |                   |  |
| subjects affected / exposed        | 22 / 246 (8.94%)  | 27 / 255 (10.59%) |  |
| occurrences (all)                  | 24                | 36                |  |
| Staphylococcal bacteraemia         |                   |                   |  |
| subjects affected / exposed        | 20 / 246 (8.13%)  | 17 / 255 (6.67%)  |  |
| occurrences (all)                  | 23                | 20                |  |
| Metabolism and nutrition disorders |                   |                   |  |
| Decreased appetite                 |                   |                   |  |
| subjects affected / exposed        | 72 / 246 (29.27%) | 91 / 255 (35.69%) |  |
| occurrences (all)                  | 89                | 109               |  |
| Dehydration                        |                   |                   |  |
| subjects affected / exposed        | 13 / 246 (5.28%)  | 13 / 255 (5.10%)  |  |
| occurrences (all)                  | 31                | 16                |  |
| Diabetes mellitus                  |                   |                   |  |
| subjects affected / exposed        | 17 / 246 (6.91%)  | 8 / 255 (3.14%)   |  |
| occurrences (all)                  | 19                | 8                 |  |
| Fluid overload                     |                   |                   |  |
| subjects affected / exposed        | 11 / 246 (4.47%)  | 14 / 255 (5.49%)  |  |
| occurrences (all)                  | 16                | 14                |  |
| Hyperglycaemia                     |                   |                   |  |

|                             |                    |                    |
|-----------------------------|--------------------|--------------------|
| subjects affected / exposed | 54 / 246 (21.95%)  | 66 / 255 (25.88%)  |
| occurrences (all)           | 81                 | 90                 |
| Hyperkalaemia               |                    |                    |
| subjects affected / exposed | 30 / 246 (12.20%)  | 23 / 255 (9.02%)   |
| occurrences (all)           | 43                 | 40                 |
| Hypocalcaemia               |                    |                    |
| subjects affected / exposed | 28 / 246 (11.38%)  | 37 / 255 (14.51%)  |
| occurrences (all)           | 51                 | 58                 |
| Hypoalbuminaemia            |                    |                    |
| subjects affected / exposed | 24 / 246 (9.76%)   | 30 / 255 (11.76%)  |
| occurrences (all)           | 53                 | 43                 |
| Hyperuricaemia              |                    |                    |
| subjects affected / exposed | 15 / 246 (6.10%)   | 10 / 255 (3.92%)   |
| occurrences (all)           | 17                 | 14                 |
| Hypokalaemia                |                    |                    |
| subjects affected / exposed | 92 / 246 (37.40%)  | 83 / 255 (32.55%)  |
| occurrences (all)           | 140                | 120                |
| Hypomagnesaemia             |                    |                    |
| subjects affected / exposed | 113 / 246 (45.93%) | 113 / 255 (44.31%) |
| occurrences (all)           | 168                | 157                |
| Hyponatraemia               |                    |                    |
| subjects affected / exposed | 26 / 246 (10.57%)  | 25 / 255 (9.80%)   |
| occurrences (all)           | 32                 | 42                 |
| Hypophosphataemia           |                    |                    |
| subjects affected / exposed | 24 / 246 (9.76%)   | 27 / 255 (10.59%)  |
| occurrences (all)           | 28                 | 30                 |



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date            | Amendment   |
|-----------------|---|
| 01 October 2013 | The changes include: Removal of all language referencing the donor sub-study. Added to Inclusion Criteria No. 10: clarification that male subjects and their female spouse/partners who are of child bearing potential must be using diaphragms or condoms starting at Screening and continue through the treatment period and for 90 days after the final study drug administration. Added details to Exclusion Criteria No. 10: the components of the vaccine aminoglycoside antibiotics (kanamycin and the like used for the vaccine production). Added to Exclusion Criteria No. 13: Other subjects considered ineligible by the investigator/sub-investigator. Removal of all language referencing the Home Health Care (HHC) provider and procedures. Added a detailed table to show the time ranges of the specific examinations, observations, etc. Removal of specific language referencing portions of the PGx sub-study procedures that will not be followed in Japan. Removal of references that study drug should be returned to the sponsor or depot. Removed references to drug may be destroyed at the study center. Added that the head of the study drug store manager should take responsibility for the accountability, storage, inventory, reconciliation and returns. Removed the option to have others designated by the Sponsor perform subject unblinding. Revised SAE reporting contact information. Revised who is responsible for submitting expedited reports to the Japanese authorities. Revised that the investigator will report SAEs to the head of the study center and ensure reporting to JUTOKUNA YUUGAIJISHOU. Responsibilities of the investigator were added to judge when the follow up of an SAE is no longer necessary. Responsibilities of the study center head were added with regards to obtaining and reporting new information on serious and unexpected adverse reactions. Added in the always report as serious list to the study appendices. |
| 01 October 2013 | The changes include: Added additional actions for the investigator to take when they do not follow the protocol for medically inevitable reasons in order to avoid urgent risks for subjects. Deleted the rest of world confidentiality language and added Japan confidentiality language. Deleted the rest of world publication language and added Japan publication language. Deleted the rest of world insurance language and procedures and added Japan insurance language.   |

|               |  |
|---------------|--|
| 28 March 2014 | <p>The changes include: Added Multi Gated Acquisition Scan (MUGA) as an acceptable procedure to determine HCT-CI criteria. Revised language to indicate that the first dose of study drug can now be administered within 72 hours prior to the start of conditioning therapy. Added language to state that the platelet count must be greater than or equal to 50,000 mm<sup>3</sup> within 3 days prior to all study drug injections, and added clarification that results must be converted to SI units. Added language for donating peripheral stem cells prior to the initiation of mobilization therapy (eg G-CSF) for the purpose of donor blood sample collection. Added criteria and methods language regarding the planned futility analyses. Added language to Inclusion Criteria 4 to state acceptable alleles crossmatch typing. Added language to Inclusion Criteria 6 (g)(i) to specify how refractory anemia is defined. Removed Wingard reference. Added language allowing serum pregnancy testing at Screening and subsequent testing days. Specified that the birth control requirement is for heterosexually active participants. Moved language regarding acceptable forms of birth control to another inclusion criterion and increased the duration of birth control use while in the study. Added language regarding acceptable forms of birth control and male sterilization and increased duration of birth control use while in the study. Revised language to increase duration of birth control use while in the study. Revised the HCT-CI score to exclude subjects that have a comorbidity score of <math>\geq 4</math>. Specified Polymerase Chain Reaction (PCR) as the type of hepatitis C RNA. Added a statement to clarify components used in manufacturing of the vaccine, kanamycin. Added that cord transplants and haploidentical transplant subjects are excluded because they are expected to have reduced response to ASP0113. Added that subjects with a platelet count of less than 50,000 mm<sup>3</sup> within 3 days prior to randomization are excl</p>              |
| 28 March 2014 | <p>The changes include: Added that subjects with aplastic anemia or multiple myeloma are excluded. In the Treatment and Study Discontinuation Section, added the criteria that subjects that fail to receive one or more doses of study drug after the first injection but are able to continue in the trial, should not be terminated. Also, included the criteria to allow the PI to use their medical discretion in determining whether a subject should continue with study drug treatment and/or the study. In the Treatment Only Discontinuation Section, added criteria regarding anaphylaxis, seizure, and participation in other interventional trials. Also revised language to clarify follow-up visit requirements for safety reporting purposes. Added instructions of the process for subjects that receive at least one dose of study drug, but do not complete the vaccination regimen. Added language stating that intravenous dose of Aciclovir may be rounded up to the nearest 100 mg. Revised value for the protocol-defined CMV viral load to 1000 IU/mL. a) Revised and added language to allow the Screening visit and Visit 2 to occur on the same day, b) allow the use of local laboratory results to determine eligibility at the Screening Visit, and c) to outline the rescreen/repeat lab parameters during the Screening Period. Added language to state that Screening safety laboratory assessments are to be completed by the local laboratory and beginning at Visit 2, all laboratory assessment are to be completed by the central laboratory. Added row to Table 1 for Karnofsky Performance scale and text to clearly state this will be assessed at Visits 2, 5, 7, 9, 11, 13, and 14. Increased the window to <math>\pm 4</math> days for the CMV &amp; GVHD assessments on Day 7/Week 1(A1). Added a window of <math>\pm 10</math> minutes for vital signs and reactogenicity evaluations done 60 minutes after injection. Revised language regarding length of time concomitant medication information will be captured after the last administration of study drug.</p> |

|                  |   |
|------------------|---|
| 28 March 2014    | The changes include: Removed the optional Abbott whole blood sub-study. Added additional data points to be collected regarding transplant information, such as volume infused, donor race and ethnicity. Added language regarding SAE reporting requirements during the long-term follow-up period. Added language regarding non-clinical data. Clarify by what method the vaccine schedule was determined. Removed first bullet regarding an exploratory analysis and revised language in appendix. Added language to indicate current regulatory status of the Abbott device being used for CMV viral load testing. Removed language related to how to record the grade of GVHD and added a bullet to indicate how to assess chronic GVHD. Added language to indicate how to capture the day of engraftment. Revised language to indicate the information that will be collected by the site on the HEA. Total blood volume to be collected for the study is increased. Added language to include the Data Monitoring Committee's responsibilities and planned futility analysis. Revised language for the potential of additional components to be incorporated into the composite endpoint. Added reference and include table of protocol defined definitions of comorbidities for the HCT-Comorbidity Index. Revised definition of CMV Retinitis diagnosis to include in vitreous fluid by culture or PCR. Revised language to remove the last sub-bullet in the list regarding all cause mortalities excluding the expected adverse drug reactions (ADRs) with a fatal outcome.                   |
| 20 May 2014      | The changes include: Section III – List of Abbreviations and Key Terms-Added MUGA Multi Gated Acquisition Scan Modified HCT-CI Score- Amended to "The subject's Modified HCT-CI score should must be determined during the Screening period using the history and laboratory results obtained on the day of Screening. Pulmonary function tests (PFTs), multi gated acquisition scans (MUGAs), and/or echocardiograms performed within 6 months (180 days) prior to Screening can be used for scoring pulmonary and cardiac comorbidities."Modified HCT-CI Comorbidity Definitions and Scores - Amended to"*Pulmonary function tests (PFTs), multi gated acquisition scans (MUGAs), and/or echocardiograms performed within 6 months (180 days) prior to Screening may be used for scoring pulmonary and cardiac comorbidities." When assessing Renal function, to convert creatinine from micromoles per liter (Umore/L) to milligrams per deciliter (mg/dL), divide micromoles per liter by 88.4 (Umore/L ÷ 88.4 = mg/dL). The definitions for each comorbidity based on definitions published by Sorror in 2013 are provided below: Protocol Defined Definitions of Comorbidities for the HCT-Comorbidity Index. Arrhythmia (score 1): Any type of arrhythmia that has necessitated the delivery of a specific anti-arrhythmia treatment at any time in the patient's past medical history. A score is assigned even if the patient was in normal sinus rhythm at the time of data acquisition or at the landmark date. No score is assigned to transient arrhythmias that never required treatment. |
| 04 December 2015 | The changes include: Parts 1 and 2 of the study design are merged into a single 1-part study. Composite endpoint of overall mortality and cytomegalovirus (CMV) end organ disease (EOD) through 1 year post-transplant will be assessed as a primary endpoint. Incidence of grade 3 treatment-emergent infections other than CMV and Time to Grade 3 treatment emergent infections other than CMV were reclassified from secondary to exploratory endpoints. Clarity provided regarding discontinuation subjects who are enrolled in the study and for whom study treatment is permanently discontinued prematurely for any reason. Specify that approximately 500 subjects will be enrolled and receive study drug in the study. Specify that with respect to incidence of other efficacy-related clinical outcomes, subjects with insufficient data to determine status will be assumed to have had the event in question.  |
| 04 August 2016   | The changes include: All women < 50 years of age who are not documented to be surgically sterile must have a negative urine or serum pregnancy test at screening and prior to each dose.  |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

In Oct 2014 data monitoring committee informed Astellas of the results of the first futility analysis. The FDA considered data for 68 participants included in futility analysis compromised and asked that it is not included in final efficacy analysis.

Notes: