



## Clinical trial results:

### A Randomized, Open-label, Phase 3 Study of Carfilzomib Plus Dexamethasone Versus Bortezomib Plus Dexamethasone in Patients With Relapsed Multiple Myeloma

#### Summary

|                          |                                     |
|--------------------------|-------------------------------------|
| EudraCT number           | 2012-000128-16                      |
| Trial protocol           | BE GB HU DE IT ES SK GR CZ AT BG PL |
| Global end of trial date | 05 February 2018                    |

#### Results information

|                                |                  |
|--------------------------------|------------------|
| Result version number          | v1 (current)     |
| This version publication date  | 13 February 2019 |
| First version publication date | 13 February 2019 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | 2011-003 |
|-----------------------|----------|

##### Additional study identifiers

|                                    |                          |
|------------------------------------|--------------------------|
| ISRCTN number                      | -                        |
| ClinicalTrials.gov id (NCT number) | NCT01568866              |
| WHO universal trial number (UTN)   | -                        |
| Other trial identifiers            | 20130398: Amgen Study ID |

Notes:

##### Sponsors

|                              |   |
|------------------------------|---|
| Sponsor organisation name    | Amgen Inc.  |
| Sponsor organisation address | One Amgen Center Drive, Thousand Oaks, CA, United States, 91320                       |
| Public contact               | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com |
| Scientific contact           | IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com |

Notes:

##### Paediatric regulatory details

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

Notes:

## Results analysis stage

|  |                  |
|--|------------------|
| Analysis stage                                       | Final            |
| Date of interim/final analysis                       | 05 February 2018 |
| Is this the analysis of the primary completion data? | No               |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 05 February 2018 |
| 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 compare progression-free survival in patients with multiple myeloma who relapsed after 1 to 3 prior therapies treated with carfilzomib plus dexamethasone or bortezomib plus dexamethasone.

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and in a manner consistent with Good Clinical Practice (GCP) guidelines and applicable regulatory requirements. The protocol, protocol amendments, protocol clarification letters, informed consent forms (ICFs), subject dosing diaries, advertisements, and health-related quality of life (HRQL) questionnaires were submitted to each study center's Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Written informed consent was obtained from all potential subjects (or legal representatives in the event the subject was unable to sign) prior to any study-specific procedures being conducted.

Background therapy: -

Evidence for comparator: -

|   |              |
|---|--------------|
| Actual start date of recruitment                          | 20 June 2012 |
| Long term follow-up planned                               | Yes          |
| Long term follow-up rationale                             | Efficacy     |
| Long term follow-up duration                              | 72 Months    |
| Independent data monitoring committee (IDMC) involvement? | Yes          |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Australia: 81          |
| Country: Number of subjects enrolled | Japan: 44              |
| Country: Number of subjects enrolled | Korea, Republic of: 16 |
| Country: Number of subjects enrolled | New Zealand: 23        |
| Country: Number of subjects enrolled | Singapore: 20          |
| Country: Number of subjects enrolled | Taiwan: 24             |
| Country: Number of subjects enrolled | Thailand: 5            |
| Country: Number of subjects enrolled | Bulgaria: 22           |
| Country: Number of subjects enrolled | Czech Republic: 72     |
| Country: Number of subjects enrolled | Hungary: 28            |
| Country: Number of subjects enrolled | Israel: 22             |
| Country: Number of subjects enrolled | Poland: 27             |
| Country: Number of subjects enrolled | Romania: 5             |
| Country: Number of subjects enrolled | Russian Federation: 44 |

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Slovakia: 1        |
| Country: Number of subjects enrolled | Ukraine: 35        |
| Country: Number of subjects enrolled | Canada: 38         |
| Country: Number of subjects enrolled | United States: 46  |
| Country: Number of subjects enrolled | Brazil: 25         |
| Country: Number of subjects enrolled | Austria: 5         |
| Country: Number of subjects enrolled | Belgium: 27        |
| Country: Number of subjects enrolled | France: 68         |
| Country: Number of subjects enrolled | Germany: 44        |
| Country: Number of subjects enrolled | Greece: 38         |
| Country: Number of subjects enrolled | Italy: 80          |
| Country: Number of subjects enrolled | Spain: 60          |
| Country: Number of subjects enrolled | United Kingdom: 29 |
| Worldwide total number of subjects   | 929                |
| EEA total number of subjects         | 506                |

Notes:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| In utero                                  | 0   |
| Preterm newborn - gestational age < 37 wk | 0   |
| Newborns (0-27 days)                      | 0   |
| Infants and toddlers (28 days-23 months)  | 0   |
| Children (2-11 years)                     | 0   |
| Adolescents (12-17 years)                 | 0   |
| Adults (18-64 years)                      | 433 |
| From 65 to 84 years                       | 487 |
| 85 years and over                         | 9   |

## Subject disposition

### Recruitment

Recruitment details:

Adults with relapsed multiple myeloma were enrolled between 20 June 2012 and 30 June 2014 at 198 centers in 27 countries in Europe, North America, South America, and the Asia-Pacific region.

### Pre-assignment

Screening details:

Randomization was stratified by previous proteasome inhibitor therapy (yes vs no), previous lines of treatment (1 vs 2 or 3), International Staging System stage (I vs II-III), and planned route of bortezomib administration (intravenous vs subcutaneous) if randomly assigned to the bortezomib group.

### Period 1

|                              |                                |
|------------------------------|--------------------------------|
| Period 1 title               | Overall Study (overall period) |
| Is this the baseline period? | Yes                            |
| Allocation method            | Randomised - controlled        |
| Blinding used                | Not blinded                    |

### Arms

|                              |                  |
|------------------------------|------------------|
| Are arms mutually exclusive? | Yes              |
| <b>Arm title</b>             | Bortezomib + DEX |

Arm description:

Participants received bortezomib 1.3 mg/m<sup>2</sup> administered intravenously (IV) or subcutaneously (SC) on Days 1, 4, 8, and 11 of a 21-day cycle plus dexamethasone (DEX) 20 mg administered on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle.

|  |  |
|--|--|
| Arm type                               | Active comparator                          |
| Investigational medicinal product name | Bortezomib                                 |
| Investigational medicinal product code |  |
| Other name                             | Velcade                                    |
| Pharmaceutical forms                   | Powder for solution for injection/infusion |
| Routes of administration               | Subcutaneous use, Intravenous bolus use    |

Dosage and administration details:

Bortezomib is administered as a 3-5 second bolus IV injection or SC injection (in accordance with regulatory approval)

|                  |                   |
|------------------|-------------------|
| <b>Arm title</b> | Carfilzomib + DEX |
|------------------|-------------------|

Arm description:

Participants received 20 mg/m<sup>2</sup> carfilzomib administered by IV infusion on Days 1 and 2 of Cycle 1, followed by 56 mg/m<sup>2</sup> on Days 8, 9, 15, and 16 of Cycle 1 and for each 28-day cycle thereafter. Additionally, participants received 20 mg dexamethasone on Days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28 day cycle.

|  |                                   |
|--|-----------------------------------|
| Arm type                               | Experimental                      |
| Investigational medicinal product name | Carfilzomib                       |
| Investigational medicinal product code | PR171                             |
| Other name                             | Kyprolis                          |
| Pharmaceutical forms                   | Powder for solution for injection |
| Routes of administration               | Intravenous use                   |

Dosage and administration details:

Carfilzomib is administered over 30 minutes as an infusion.

| <b>Number of subjects in period 1</b> | Bortezomib + DEX | Carfilzomib + DEX |
|---------------------------------------|------------------|-------------------|
| Started                               | 465              | 464               |
| Received Treatment                    | 456              | 463               |
| Completed                             | 0                | 0                 |
| Not completed                         | 465              | 464               |
| Adverse event, serious fatal          | 11               | 19                |
| Physician decision                    | 40               | 32                |
| Consent withdrawn by subject          | 19               | 13                |
| Adverse event, non-fatal              | 96               | 101               |
| Unknown                               | 1                | -                 |
| Study terminated by sponsor           | 15               | 29                |
| Randomized but Not Dosed              | 9                | 1                 |
| Patient Request                       | 57               | 72                |
| Protocol Non-compliance               | 2                | 4                 |
| Lost to follow-up                     | 1                | -                 |
| Disease Progression                   | 214              | 193               |

## Baseline characteristics

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Bortezomib + DEX |
|-----------------------|------------------|

Reporting group description:

Participants received bortezomib 1.3 mg/m<sup>2</sup> administered intravenously (IV) or subcutaneously (SC) on Days 1, 4, 8, and 11 of a 21-day cycle plus dexamethasone (DEX) 20 mg administered on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle.

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Carfilzomib + DEX |
|-----------------------|-------------------|

Reporting group description:

Participants received 20 mg/m<sup>2</sup> carfilzomib administered by IV infusion on Days 1 and 2 of Cycle 1, followed by 56 mg/m<sup>2</sup> on Days 8, 9, 15, and 16 of Cycle 1 and for each 28-day cycle thereafter. Additionally, participants received 20 mg dexamethasone on Days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28 day cycle.

| Reporting group values   | Bortezomib + DEX | Carfilzomib + DEX | Total |
|--|------------------|-------------------|-------|
| Number of subjects   | 465              | 464               | 929   |
| Age, Customized<br>Units: Subjects   |                  |                   |       |
| < 65 years   | 210              | 223               | 433   |
| 65 -74 years   | 189              | 164               | 353   |
| ≥ 75 years   | 66               | 77                | 143   |
| Age Continuous<br>Units: years   |                  |                   |       |
| median   | 65.0             | 65.0              |       |
| full range (min-max)   | 30.0 to 88.0     | 35.0 to 89.0      | -     |
| Sex: Female, Male<br>Units: Subjects   |                  |                   |       |
| Female   | 236              | 224               | 460   |
| Male   | 229              | 240               | 469   |
| Race/Ethnicity, Customized<br>Units: Subjects  |                  |                   |       |
| White  | 353              | 348               | 701   |
| Black  | 9                | 8                 | 17    |
| Asian  | 57               | 56                | 113   |
| Native Hawaiian/Other Pacific Islander   | 0                | 2                 | 2     |
| Not Reported   | 45               | 50                | 95    |
| Multiple   | 1                | 0                 | 1     |
| Eastern Cooperative Oncology Group (ECOG) Performance Status   |                  |                   |       |
| Eastern Cooperative Oncology Group (ECOG) Performance Status is used by doctors and researchers to assess how a participant's disease is progressing, assess how the disease affects the daily living activities of the participant and determine appropriate treatment and prognosis. 0 = Fully Active; 1 = Restricted activity but ambulatory; 2 = Ambulatory but unable to carry out work activities; 3 = Limited Self-Care; 4 = Completely Disabled, no self-care, confined to bed or chair; 5 = Dead. |                  |                   |       |
| Units: Subjects  |                  |                   |       |
| 0 (Fully active)   | 232              | 221               | 453   |
| 1 (Restrictive but ambulatory)   | 203              | 211               | 414   |
| 2 (Ambulatory but unable to work)  | 30               | 32                | 62    |
| Stratification Factor: Prior Proteasome Inhibitor Treatment  |                  |                   |       |

|   |     |     |     |
|---|-----|-----|-----|
| Units: Subjects   |     |     |     |
| Carfilzomib or bortezomib   | 253 | 252 | 505 |
| No prior carfilzomib or bortezomib  | 212 | 212 | 424 |
| Stratification Factor: Lines of Prior Treatment   |     |     |     |
| Units: Subjects   |     |     |     |
| 1 line  | 229 | 231 | 460 |
| 2 or 3 lines  | 236 | 233 | 469 |
| Stratification Factor: International Staging System (ISS) Stage   |     |     |     |
| The International Staging System (ISS) for myeloma was published by the International Myeloma Working Group: - Stage I: $\beta 2$ -microglobulin ( $\beta 2M$ ) < 3.5 mg/L, albumin $\geq$ 3.5 g/dL - Stage II: $\beta 2M$ < 3.5 mg/L and albumin < 3.5 g/dL; or $\beta 2M$ 3.5 mg/L - 5.5 mg/L irrespective of the serum albumin - Stage III: $\beta 2M \geq$ 5.5 mg/L                       |     |     |     |
| Units: Subjects   |     |     |     |
| Stage I   | 204 | 205 | 409 |
| Stage II or III   | 261 | 259 | 520 |
| Stratification Factor: Route of Bortezomib Administration   |     |     |     |
| The route of bortezomib administration (IV versus SC) was made in accordance with local regulatory approved route of administration. The value for this variable was selected for all participants prior to randomization to treatment group in order to balance the baseline characteristics that led to the choice of the particular route of bortezomib administration between the 2 arms. |     |     |     |
| Units: Subjects   |     |     |     |
| Intravenous   | 108 | 108 | 216 |
| Subcutaneous  | 357 | 356 | 713 |

## End points

### End points reporting groups

|  |                   |
|--|-------------------|
| Reporting group title  | Bortezomib + DEX  |
| Reporting group description:<br>Participants received bortezomib 1.3 mg/m <sup>2</sup> administered intravenously (IV) or subcutaneously (SC) on Days 1, 4, 8, and 11 of a 21-day cycle plus dexamethasone (DEX) 20 mg administered on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle.   |                   |
| Reporting group title  | Carfilzomib + DEX |
| Reporting group description:<br>Participants received 20 mg/m <sup>2</sup> carfilzomib administered by IV infusion on Days 1 and 2 of Cycle 1, followed by 56 mg/m <sup>2</sup> on Days 8, 9, 15, and 16 of Cycle 1 and for each 28-day cycle thereafter. Additionally, participants received 20 mg dexamethasone on Days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28 day cycle. |                   |

### Primary: Progression-free Survival

|   |                           |
|---|---------------------------|
| End point title   | Progression-free Survival |
| End point description:<br>Progression-free survival (PFS) was defined as the time from randomization to the earlier of disease progression or death due to any cause. Participants were evaluated for disease response and progression according to the International Myeloma Working Group-Uniform Response Criteria (IMWG-URC) as assessed by an Independent Review Committee (IRC). Median PFS was estimated using the Kaplan-Meier method. Participants with no baseline disease assessments, starting a new anticancer therapy before documentation of disease progression or death, death or disease progression immediately after more than 1 consecutively missed disease assessment visit, or alive without documentation of disease progression before the data cut-off date were censored. "99999" indicates data that could not be estimated. |                           |
| End point type  | Primary                   |
| End point timeframe:<br>From randomization until the data cut-off date of 10 November 2014; median follow-up time for PFS was 11.1 and 11.9 months in the bortezomib and carfilzomib arms respectively  |                           |

| End point values                 | Bortezomib + DEX  | Carfilzomib + DEX    |  |  |
|----------------------------------|-------------------|----------------------|--|--|
| Subject group type               | Reporting group   | Reporting group      |  |  |
| Number of subjects analysed      | 465               | 464                  |  |  |
| Units: months                    |                   |                      |  |  |
| median (confidence interval 95%) | 9.4 (8.4 to 10.4) | 18.7 (15.6 to 99999) |  |  |

### Statistical analyses

|  |                                       |
|--|---------------------------------------|
| Statistical analysis title   | Analysis of Progression-free Survival |
| Statistical analysis description:<br>The hazard ratio (carfilzomib/bortezomib) was estimated using a Cox proportional hazards model stratified by prior proteasome inhibitor treatment, lines of prior treatment, ISS stage, and choice of route of bortezomib administration. |                                       |
| Comparison groups  | Bortezomib + DEX v Carfilzomib + DEX  |



|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 929                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[1]</sup> |
| P-value                                 | < 0.0001 <sup>[2]</sup>    |
| Method                                  | Stratified Log Rank        |
| Parameter estimate                      | Hazard ratio (HR)          |
| Point estimate                          | 0.533                      |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 0.437                      |
| upper limit                             | 0.651                      |

Notes:

[1] - The PFS interim analysis was to be performed using a group sequential monitoring plan. The monitoring plan included an O'Brien-Fleming type of efficacy stopping boundary constructed using the Lan-DeMets alpha spending function to ensure a 1-sided Type I error rate  $\leq 0.025$ .

[2] - Log rank test stratified by the randomization stratification factors.

## Secondary: Overall Survival

|                 |                  |
|-----------------|------------------|
| End point title | Overall Survival |
|-----------------|------------------|

End point description:

Overall survival (OS) is defined as the time from randomization to the date of death (whatever the cause). Participants who were alive or lost to follow-up as of the data analysis cut-off date were censored at the patient's date of last contact (last known to be alive). Median overall survival was estimated using the Kaplan-Meier method. "99999" indicates data that could not be estimated.

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

End point timeframe:

From randomization until the data cut-off date of 03 January 2017; median follow-up time for OS was 36.9 and 37.5 months for each treatment group respectively.

| End point values                 | Bortezomib + DEX    | Carfilzomib + DEX    |  |  |
|----------------------------------|---------------------|----------------------|--|--|
| Subject group type               | Reporting group     | Reporting group      |  |  |
| Number of subjects analysed      | 465                 | 464                  |  |  |
| Units: months                    |                     |                      |  |  |
| median (confidence interval 95%) | 40.0 (32.6 to 42.3) | 47.6 (42.5 to 99999) |  |  |

## Statistical analyses

|                            |                              |
|----------------------------|------------------------------|
| Statistical analysis title | Analysis of Overall Survival |
|----------------------------|------------------------------|

Statistical analysis description:

The second interim analysis of overall survival was to be conducted after 394 events had been reached. A one-sided significance level was determined using the O'Brien-Fleming-type  $\alpha$  spending function based on the actual number of events ( $\alpha=0.0123$ ). The hazard ratio (carfilzomib/bortezomib) was estimated using a Cox proportional hazards model stratified by prior proteasome inhibitor treatment, lines of prior treatment, ISS stage, and choice of route of bortezomib administration.

|                   |                                      |
|-------------------|--------------------------------------|
| Comparison groups | Bortezomib + DEX v Carfilzomib + DEX |
|-------------------|--------------------------------------|

|   |                            |
|---|----------------------------|
| Number of subjects included in analysis | 929                        |
| Analysis specification                  | Pre-specified              |
| Analysis type                           | superiority <sup>[3]</sup> |
| P-value                                 | = 0.01 <sup>[4]</sup>      |
| Method                                  | Stratified Log Rank        |
| Parameter estimate                      | Hazard ratio (HR)          |
| Point estimate                          | 0.791                      |
| Confidence interval                     |                            |
| level                                   | 95 %                       |
| sides                                   | 2-sided                    |
| lower limit                             | 0.648                      |
| upper limit                             | 0.964                      |

Notes:

[3] - The multiplicity in testing secondary endpoints was adjusted per group using the sequential Holm procedure to preserve the family-wise error rate at 0.025.

[4] - Log rank test stratified by the randomization stratification factors.

## Secondary: Overall Response

|   |                  |
|---|------------------|
| End point title   | Overall Response |
| End point description:  |                  |
| Disease response was evaluated according to the IMWG-URC by the IRC. Overall response was defined as the percentage of participants with a best overall response of partial response (PR), very good PR (VGPR), complete response (CR) or stringent CR (sCR). |                  |
| sCR: As for CR, normal serum free light chain (SFLC) ratio and no clonal cells in bone marrow (BM).   |                  |
| CR: No immunofixation on serum and urine, disappearance of any soft tissue plasmacytomas and < 5% plasma cells in BM biopsy;  |                  |
| VGPR: Serum and urine M-protein detectable by immunofixation but not electrophoresis or ≥ 90% reduction in serum M-protein with urine M-protein <100 mg/24 hours. A ≥ 50% reduction in the size of soft tissue plasmacytomas if present at baseline.          |                  |
| PR: ≥ 50% reduction of serum M-protein and reduction in urine M-protein by ≥ 90% or to < 200 mg/24 hours. A ≥ 50% reduction in the size of soft tissue plasmacytomas if present at baseline.  |                  |
| End point type  | Secondary        |
| End point timeframe:  |                  |
| Disease response was assessed every 28 days until end of treatment or the data cut-off date of 10 November 2014; median duration of treatment was 27 weeks in the bortezomib group and 40 weeks in the carfilzomib treatment group.                           |                  |

| End point values                  | Bortezomib + DEX    | Carfilzomib + DEX   |  |  |
|-----------------------------------|---------------------|---------------------|--|--|
| Subject group type                | Reporting group     | Reporting group     |  |  |
| Number of subjects analysed       | 465                 | 464                 |  |  |
| Units: percentage of participants |                     |                     |  |  |
| number (confidence interval 95%)  | 62.6 (58.0 to 67.0) | 76.9 (72.8 to 80.7) |  |  |

## Statistical analyses

|  |                              |
|--|------------------------------|
| Statistical analysis title   | Analysis of Overall Response |
| Statistical analysis description:  |                              |
| The odds ratio (carfilzomib/bortezomib) was calculated using the Cochran-Mantel-Haenszel method stratified by prior proteasome inhibitor treatment, lines of prior treatment, ISS stage, and choice of route of bortezomib administration. |                              |

|   |                                      |
|---|--------------------------------------|
| Comparison groups                       | Bortezomib + DEX v Carfilzomib + DEX |
| Number of subjects included in analysis | 929                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           | superiority <sup>[5]</sup>           |
| P-value                                 | < 0.0001 <sup>[6]</sup>              |
| Method                                  | Stratified Cochran-Mantel-Haenszel   |
| Parameter estimate                      | Odds ratio (OR)                      |
| Point estimate                          | 2.032                                |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | 1.519                                |
| upper limit                             | 2.718                                |

Notes:

[5] - The multiplicity in testing secondary endpoints was adjusted per group using the sequential Holm procedure to preserve the family-wise error rate at 0.025.

[6] - Cochran-Mantel-Haenszel test stratified by the randomization stratification factors.

## Secondary: Duration of Response

|                 |                      |
|-----------------|----------------------|
| End point title | Duration of Response |
|-----------------|----------------------|

End point description:

Duration of response (DOR) was calculated for participants who achieved an sCR, CR, VGPR, or PR. Duration of response is defined as the time from first evidence of PR or better to confirmation of disease progression or death due to any cause. Median duration of response was estimated using the Kaplan-Meier method. Participants with no baseline disease assessments, starting a new anticancer therapy before documentation of disease progression or death, death or disease progression immediately after more than 1 consecutively missed disease assessment visit, or alive without documentation of disease progression before the data cut-off date were censored. "99999" indicates data that could not be estimated.

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

End point timeframe:

From randomization until the data cut-off date of 10 November 2014; median follow-up time for DOR was 9.4 and 10.4 months for each treatment group respectively.

| End point values                 | Bortezomib + DEX   | Carfilzomib + DEX    |  |  |
|----------------------------------|--------------------|----------------------|--|--|
| Subject group type               | Reporting group    | Reporting group      |  |  |
| Number of subjects analysed      | 291                | 357                  |  |  |
| Units: months                    |                    |                      |  |  |
| median (confidence interval 95%) | 10.4 (9.3 to 13.8) | 21.3 (21.3 to 99999) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Percentage of Participants with ≥ Grade 2 Peripheral Neuropathy

|                 |   |
|-----------------|---|
| End point title | Percentage of Participants with ≥ Grade 2 Peripheral Neuropathy |
|-----------------|---|

**End point description:**

Neuropathy events were defined as Grade 2 or higher peripheral neuropathy as specified by peripheral neuropathy Standardised Medical Dictionary for Regulatory Activities (MedDRA) Query, narrow (scope) (SMQN) terms. Peripheral neuropathy was assessed by neurologic exam and graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03:

Grade 1: Asymptomatic;  
 Grade 2: Moderate symptoms, limiting instrumental activities of daily living (ADL)  
 Grade 3: Severe symptoms; limiting self-care ADL;  
 Grade 4: Life-threatening consequences, urgent intervention indicated;  
 Grade 5: Death.

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

**End point timeframe:**

From the first dose of study drug up to 30 days after the last dose of study drug as of the data cut-off date of 10 November 2014; median duration of treatment was 27 weeks in the bortezomib group and 40 weeks in the carfilzomib treatment group.

| End point values                  | Bortezomib + DEX    | Carfilzomib + DEX |  |  |
|-----------------------------------|---------------------|-------------------|--|--|
| Subject group type                | Reporting group     | Reporting group   |  |  |
| Number of subjects analysed       | 456                 | 463               |  |  |
| Units: percentage of participants |                     |                   |  |  |
| number (confidence interval 95%)  | 32.0 (27.7 to 36.3) | 6.0 (3.9 to 8.2)  |  |  |

**Statistical analyses**

|                                   |                                   |
|-----------------------------------|-----------------------------------|
| <b>Statistical analysis title</b> | Analysis of Peripheral Neuropathy |
|-----------------------------------|-----------------------------------|

**Statistical analysis description:**

The odds ratio (carfilzomib/bortezomib) was estimated using the unconditional Cochran-Mantel-Haenszel method.

|   |                                      |
|---|--------------------------------------|
| Comparison groups                       | Bortezomib + DEX v Carfilzomib + DEX |
| Number of subjects included in analysis | 919                                  |
| Analysis specification                  | Pre-specified                        |
| Analysis type                           | superiority <sup>[7]</sup>           |
| P-value                                 | < 0.0001                             |
| Method                                  | Cochran-Mantel-Haenszel              |
| Parameter estimate                      | Odds ratio (OR)                      |
| Point estimate                          | 0.137                                |
| Confidence interval                     |                                      |
| level                                   | 95 %                                 |
| sides                                   | 2-sided                              |
| lower limit                             | 0.089                                |
| upper limit                             | 0.21                                 |

**Notes:**

[7] - The multiplicity in testing secondary endpoints was adjusted per group using the sequential Holm procedure to preserve the family-wise error rate at 0.025.

**Secondary: Percentage of Participants with a Significant Reduction in Left Ventricular Ejection Fraction (LVEF)**

|                 |  |
|-----------------|--|
| End point title | Percentage of Participants with a Significant Reduction in Left Ventricular Ejection Fraction (LVEF) |
|-----------------|--|

**End point description:**

A significant reduction in LVEF was defined as a  $\geq 10\%$  decrease (absolute change) from baseline in participants whose baseline LVEF is  $\leq 55\%$ .

For participants with LVEF  $> 55\%$  at baseline, a significant change was defined as a decrease in LVEF to  $< 45\%$ .

The analysis was based in the cardiopulmonary safety evaluable subgroup (all randomized participants who enrolled in the cardiopulmonary substudy with evaluable baseline echocardiogram scans per the central laboratory) and with both baseline and at least one post-baseline LVEF measurement within 24 weeks.

|                       |           |
|-----------------------|-----------|
| End point type        | Secondary |
| End point timeframe:  |           |
| Baseline and 24 weeks |           |

| End point values                  | Bortezomib + DEX | Carfilzomib + DEX |  |  |
|-----------------------------------|------------------|-------------------|--|--|
| Subject group type                | Reporting group  | Reporting group   |  |  |
| Number of subjects analysed       | 40               | 48                |  |  |
| Units: percentage of participants |                  |                   |  |  |
| number (not applicable)           | 2.6              | 0.0               |  |  |

**Statistical analyses**

No statistical analyses for this end point

**Secondary: Change from Baseline in Right Ventricular Fractional Area Change (FAC)**

|                 |  |
|-----------------|--|
| End point title | Change from Baseline in Right Ventricular Fractional Area Change (FAC) |
|-----------------|--|

**End point description:**

Right ventricular function was assessed by measuring fractional area change (FAC) on echocardiogram. The analysis was based on the cardiopulmonary safety evaluable subgroup with available FAC data at baseline; "n" indicates participants whose results were available at both the baseline and the specified post-baseline visit.

|   |           |
|---|-----------|
| End point type  | Secondary |
| End point timeframe:  |           |
| Baseline and Weeks 12, 24 and 36 and at end of treatment (median duration of treatment was 27 weeks in the bortezomib group and 40 weeks in the carfilzomib treatment group). |           |

| End point values                      | Bortezomib + DEX   | Carfilzomib + DEX  |  |  |
|---------------------------------------|--------------------|--------------------|--|--|
| Subject group type                    | Reporting group    | Reporting group    |  |  |
| Number of subjects analysed           | 52                 | 55                 |  |  |
| Units: percent fractional area change |                    |                    |  |  |
| arithmetic mean (standard deviation)  |                    |                    |  |  |
| Week 12 (n = 40, 40)                  | -0.7 ( $\pm$ 5.00) | -1.1 ( $\pm$ 5.36) |  |  |
| Week 24 (n = 26, 31)                  | 0.7 ( $\pm$ 6.10)  | -1.0 ( $\pm$ 5.03) |  |  |
| Week 36 (n = 15, 18)                  | -0.5 ( $\pm$ 7.27) | -0.5 ( $\pm$ 6.38) |  |  |
| End of Treatment (n = 23, 18)         | 0.4 ( $\pm$ 4.73)  | -1.9 ( $\pm$ 5.47) |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Change from Baseline in Pulmonary Artery Systolic Pressure (PASP)

|                 |   |
|-----------------|---|
| End point title | Change from Baseline in Pulmonary Artery Systolic Pressure (PASP) |
|-----------------|---|

End point description:

Pulmonary artery pressure was measured using transthoracic echocardiogram.

The analysis was based on the cardiopulmonary safety evaluable subgroup with available PASP data at baseline; "n" indicates participants whose results were available at both the baseline and the specified post-baseline visit.

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

End point timeframe:

Baseline and Weeks 12, 24 and 36 and at end of treatment (median duration of treatment was 27 weeks in the bortezomib group and 40 weeks in the carfilzomib treatment group).

| End point values                     | Bortezomib + DEX | Carfilzomib + DEX |  |  |
|--------------------------------------|------------------|-------------------|--|--|
| Subject group type                   | Reporting group  | Reporting group   |  |  |
| Number of subjects analysed          | 52               | 45                |  |  |
| Units: mmHg                          |                  |                   |  |  |
| arithmetic mean (standard deviation) |                  |                   |  |  |
| Week 12 (n=34, 30)                   | 0.3 (± 11.72)    | 2.8 (± 11.44)     |  |  |
| Week 24 (n=22, 20)                   | 1.7 (± 8.47)     | 3.4 (± 13.63)     |  |  |
| Week 36 (n=12, 14)                   | 4.0 (± 7.24)     | 2.6 (± 13.55)     |  |  |
| End of Treatment (n=21, 14)          | 3.4 (± 8.14)     | 0.9 (± 11.40)     |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From the first dose of study drug up to 30 days after the last dose of study drug as of the data cut-off date of 20 March 2018; median duration of treatment was 27 weeks in the bortezomib group and 48 weeks in the carfilzomib treatment group.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 20.1 |
|--------------------|------|

### Reporting groups

|                       |                  |
|-----------------------|------------------|
| Reporting group title | Bortezomib + DEX |
|-----------------------|------------------|

Reporting group description:

Participants received bortezomib 1.3 mg/m<sup>2</sup> administered intravenously (IV) or subcutaneously (SC) on Days 1, 4, 8, and 11 of a 21-day cycle plus dexamethasone (DEX) 20 mg administered on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each 21-day cycle.

|                       |                   |
|-----------------------|-------------------|
| Reporting group title | Carfilzomib + DEX |
|-----------------------|-------------------|

Reporting group description:

Participants received 20 mg/m<sup>2</sup> carfilzomib administered by IV infusion on Days 1 and 2 of Cycle 1, followed by 56 mg/m<sup>2</sup> on Days 8, 9, 15, and 16 of Cycle 1 and for each 28-day cycle thereafter. Additionally, participants received 20 mg dexamethasone on Days 1, 2, 8, 9, 15, 16, 22, and 23 of each 28 day cycle.

| Serious adverse events  | Bortezomib + DEX   | Carfilzomib + DEX  |  |
|---|--------------------|--------------------|--|
| Total subjects affected by serious adverse events                   |                    |                    |  |
| subjects affected / exposed   | 184 / 456 (40.35%) | 279 / 463 (60.26%) |  |
| number of deaths (all causes)                                       | 261                | 241                |  |
| number of deaths resulting from adverse events                      |                    |                    |  |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |                    |  |
| Acute myeloid leukaemia   |                    |                    |  |
| subjects affected / exposed   | 0 / 456 (0.00%)    | 1 / 463 (0.22%)    |  |
| occurrences causally related to treatment / all                     | 0 / 0              | 0 / 2              |  |
| deaths causally related to treatment / all                          | 0 / 0              | 1 / 1              |  |
| Adenocarcinoma of colon   |                    |                    |  |
| subjects affected / exposed   | 1 / 456 (0.22%)    | 0 / 463 (0.00%)    |  |
| occurrences causally related to treatment / all                     | 0 / 1              | 0 / 0              |  |
| deaths causally related to treatment / all                          | 0 / 0              | 0 / 0              |  |
| Basal cell carcinoma  |                    |                    |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 456 (0.00%) | 2 / 463 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bladder transitional cell carcinoma             |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cancer pain                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Carcinoma in situ                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colon cancer                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Extradural neoplasm                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metastases to spine                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oesophageal squamous cell carcinoma             |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Plasma cell myeloma                             |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 456 (0.22%) | 5 / 463 (1.08%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 5           |  |
| deaths causally related to treatment / all      | 1 / 1           | 3 / 3           |  |
| Plasmacytoma                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 5 / 463 (1.08%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pleural mesothelioma                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rectal cancer                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| 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 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tongue neoplasm malignant stage unspecified     |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vascular disorders                              |                 |                 |  |
| Aortic aneurysm                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Aortic embolus                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| Arteriosclerosis                                |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Circulatory collapse                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Deep vein thrombosis                            |                 |                 |  |
| subjects affected / exposed                     | 3 / 456 (0.66%) | 5 / 463 (1.08%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 2 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haematoma                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypertension                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 3 / 463 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 3 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypertensive crisis                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypotension                                     |                 |                 |  |
| subjects affected / exposed                     | 4 / 456 (0.88%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 4 / 4           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Malignant hypertension                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Orthostatic hypotension                         |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 4 / 456 (0.88%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 4 / 4           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peripheral arterial occlusive disease           |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peripheral vascular disorder                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Superior vena cava syndrome                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| 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 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vena cava thrombosis                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Venous thrombosis limb                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Surgical and medical procedures                 |                 |                 |  |
| Abdominal hernia repair                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Colostomy closure                               |                 |                 |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                          | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Haemorrhoid operation                                |                 |                 |  |
| subjects affected / exposed                          | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Removal of internal fixation                         |                 |                 |  |
| subjects affected / exposed                          | 1 / 456 (0.22%) | 0 / 463 (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                          | 1 / 456 (0.22%) | 2 / 463 (0.43%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 1 / 2           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Cardiac death  |                 |                 |  |
| subjects affected / exposed                          | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 1 / 1           |  |
| Chest pain   |                 |                 |  |
| subjects affected / exposed                          | 4 / 456 (0.88%) | 4 / 463 (0.86%) |  |
| occurrences causally related to treatment / all      | 2 / 4           | 0 / 4           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Death  |                 |                 |  |
| subjects affected / exposed                          | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 1 / 1           |  |
| Disease progression                                  |                 |                 |  |
| subjects affected / exposed                          | 6 / 456 (1.32%) | 9 / 463 (1.94%) |  |
| occurrences causally related to treatment / all      | 0 / 7           | 0 / 10          |  |
| deaths causally related to treatment / all           | 3 / 3           | 5 / 5           |  |
| Fatigue  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 456 (0.22%) | 3 / 463 (0.65%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| General physical health deterioration           |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 4 / 463 (0.86%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Generalised oedema                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperpyrexia                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperthermia                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Malaise   |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Non-cardiac chest pain                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oedema peripheral                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 2 / 463 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pain  |                 |                 |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (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                     | 3 / 456 (0.66%) | 19 / 463 (4.10%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 10 / 21          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Strangulated hernia                             |                 |                  |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Sudden death                                    |                 |                  |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 3 / 463 (0.65%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3            |  |
| deaths causally related to treatment / all      | 1 / 1           | 3 / 3            |  |
| Immune system disorders                         |                 |                  |  |
| Hypersensitivity                                |                 |                  |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Hypogammaglobulinaemia                          |                 |                  |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Reproductive system and breast disorders        |                 |                  |  |
| Pelvic fluid collection                         |                 |                  |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Prostatomegaly                                  |                 |                  |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| Uterine haemorrhage                             |                 |                  |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Respiratory, thoracic and mediastinal disorders |                 |                  |  |
| Acute pulmonary oedema                          |                 |                  |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 3 / 463 (0.65%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 2 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Acute respiratory distress syndrome             |                 |                  |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 1 / 463 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1            |  |
| Acute respiratory failure                       |                 |                  |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Asthma  |                 |                  |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 3 / 463 (0.65%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Bronchopneumopathy                              |                 |                  |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Chronic obstructive pulmonary disease           |                 |                  |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 2 / 463 (0.43%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Dyspnoea  |                 |                  |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 18 / 463 (3.89%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 11 / 18          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| Epistaxis                                       |                 |                  |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 1 / 463 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Hypoxia   |                 |                  |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (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                     | 0 / 456 (0.00%) | 2 / 463 (0.43%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 3 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1            |  |
| Lung disorder                                   |                 |                  |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 3 / 463 (0.65%)  |  |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 3            |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0            |  |
| Pleural effusion                                |                 |                  |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 3 / 463 (0.65%)  |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 3            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Pneumonitis                                     |                 |                  |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 3 / 463 (0.65%)  |  |
| occurrences causally related to treatment / all | 0 / 2           | 3 / 6            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Pulmonary arterial hypertension                 |                 |                  |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Pulmonary embolism                              |                 |                  |  |
| subjects affected / exposed                     | 3 / 456 (0.66%) | 10 / 463 (2.16%) |  |
| occurrences causally related to treatment / all | 2 / 3           | 5 / 10           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Pulmonary hypertension                          |                 |                  |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 456 (0.00%) | 3 / 463 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 4 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary oedema                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 2 / 463 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 2           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| Respiratory failure                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 4 / 463 (0.86%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| Upper respiratory tract inflammation            |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Psychiatric disorders                           |                 |                 |  |
| Completed suicide                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| Confusional state                               |                 |                 |  |
| subjects affected / exposed                     | 4 / 456 (0.88%) | 4 / 463 (0.86%) |  |
| occurrences causally related to treatment / all | 1 / 4           | 1 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Depression                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mental disorder                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Persistent depressive disorder                  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Psychotic disorder                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Product issues                                  |                 |                 |  |
| Device occlusion                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Thrombosis in device                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Alanine aminotransferase increased              |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Aspartate aminotransferase increased            |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood creatinine increased                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 2 / 463 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cortisol decreased                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| Influenza B virus test positive<br>subjects affected / exposed | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to<br>treatment / all             | 0 / 0           | 1 / 1           |  |
| deaths causally related to<br>treatment / all                  | 0 / 0           | 0 / 0           |  |
| Lymphocyte count decreased<br>subjects affected / exposed      | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to<br>treatment / all             | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                  | 0 / 0           | 0 / 0           |  |
| Platelet count decreased<br>subjects affected / exposed        | 3 / 456 (0.66%) | 2 / 463 (0.43%) |  |
| occurrences causally related to<br>treatment / all             | 2 / 3           | 2 / 2           |  |
| deaths causally related to<br>treatment / all                  | 0 / 0           | 0 / 0           |  |
| Troponin T increased<br>subjects affected / exposed            | 1 / 456 (0.22%) | 1 / 463 (0.22%) |  |
| occurrences causally related to<br>treatment / all             | 0 / 1           | 1 / 1           |  |
| deaths causally related to<br>treatment / all                  | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural<br>complications              |                 |                 |  |
| Chest injury   |                 |                 |  |
| subjects affected / exposed                                    | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to<br>treatment / all             | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                  | 0 / 0           | 0 / 0           |  |
| Compression fracture   |                 |                 |  |
| subjects affected / exposed                                    | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to<br>treatment / all             | 0 / 0           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                  | 0 / 0           | 0 / 0           |  |
| Facial bones fracture  |                 |                 |  |
| subjects affected / exposed                                    | 1 / 456 (0.22%) | 1 / 463 (0.22%) |  |
| occurrences causally related to<br>treatment / all             | 0 / 1           | 0 / 1           |  |
| deaths causally related to<br>treatment / all                  | 0 / 0           | 0 / 0           |  |
| Femoral neck fracture  |                 |                 |  |
| subjects affected / exposed                                    | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to<br>treatment / all             | 0 / 1           | 0 / 0           |  |
| deaths causally related to<br>treatment / all                  | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Femur fracture                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Foot fracture                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Fracture  |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Head injury                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 1 / 1           | 1 / 1           |  |
| Hip fracture                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Humerus fracture                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 3 / 463 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infusion related reaction                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 3 / 463 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 3 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ligament sprain                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pubis fracture                                  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Radius fracture                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal compression fracture                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ulna fracture                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper limb fracture                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Wound   |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Acute coronary syndrome                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 2 / 463 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute left ventricular failure                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute myocardial infarction                     |                 |                 |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 2 / 456 (0.44%) | 1 / 463 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 2           | 1 / 1            |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0            |  |
| Angina pectoris                                 |                 |                  |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 3 / 463 (0.65%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 3 / 5            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Aortic valve incompetence                       |                 |                  |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Atrial fibrillation                             |                 |                  |  |
| subjects affected / exposed                     | 4 / 456 (0.88%) | 7 / 463 (1.51%)  |  |
| occurrences causally related to treatment / all | 1 / 5           | 3 / 7            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Atrial flutter                                  |                 |                  |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Bifascicular block                              |                 |                  |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Cardiac arrest                                  |                 |                  |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 2 / 463 (0.43%)  |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 2            |  |
| deaths causally related to treatment / all      | 1 / 1           | 2 / 2            |  |
| Cardiac failure                                 |                 |                  |  |
| subjects affected / exposed                     | 3 / 456 (0.66%) | 10 / 463 (2.16%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 6 / 11           |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1            |  |
| Cardiac failure acute                           |                 |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 456 (0.22%) | 2 / 463 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 2 / 2           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| Cardiac failure congestive                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac hypertrophy                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 3 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiomyopathy                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 3 / 463 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Left ventricular dysfunction                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Left ventricular failure                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myocardial infarction                           |                 |                 |  |
| subjects affected / exposed                     | 2 / 456 (0.44%) | 5 / 463 (1.08%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 2 / 5           |  |
| deaths causally related to treatment / all      | 2 / 2           | 0 / 0           |  |
| Pericardial effusion                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pleuropericarditis                              |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Right ventricular failure                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 3 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sinus tachycardia                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Stress cardiomyopathy                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Supraventricular tachycardia                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 2 / 463 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Acquired epileptic aphasia                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Central nervous system lesion                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cerebrovascular accident                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 4 / 463 (0.86%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cognitive disorder                              |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 456 (0.22%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dementia  |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Depressed level of consciousness                |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dizziness                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Encephalopathy                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Headache  |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 2 / 463 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypercapnic coma                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypertensive encephalopathy                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ischaemic stroke                                |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 456 (0.00%) | 3 / 463 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lethargy  |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Loss of consciousness                           |                 |                 |  |
| subjects affected / exposed                     | 2 / 456 (0.44%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolic encephalopathy                        |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neuralgia                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Neuropathy peripheral                           |                 |                 |  |
| subjects affected / exposed                     | 2 / 456 (0.44%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Paraparesis                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Paraplegia                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Polyneuropathy                                  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Posterior reversible encephalopathy syndrome    |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 2 / 463 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Radiculitis brachial                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Radiculopathy                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sciatica  |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Seizure   |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal cord compression                         |                 |                 |  |
| subjects affected / exposed                     | 2 / 456 (0.44%) | 4 / 463 (0.86%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Syncope   |                 |                 |  |
| subjects affected / exposed                     | 4 / 456 (0.88%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 3 / 5           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Transient ischaemic attack                      |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 456 (0.44%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Blood and lymphatic system disorders</b>     |                 |                 |  |
| <b>Anaemia</b>                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 5 / 463 (1.08%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 3 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Febrile neutropenia</b>                      |                 |                 |  |
| subjects affected / exposed                     | 3 / 456 (0.66%) | 4 / 463 (0.86%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 3 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Haemorrhagic anaemia</b>                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Neutropenia</b>                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Plasmacytosis</b>                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Thrombocytopenia</b>                         |                 |                 |  |
| subjects affected / exposed                     | 6 / 456 (1.32%) | 4 / 463 (0.86%) |  |
| occurrences causally related to treatment / all | 3 / 6           | 4 / 7           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Thrombotic microangiopathy</b>               |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 3 / 463 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| <b>Thrombotic thrombocytopenic purpura</b>      |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ear and labyrinth disorders                     |                 |                 |  |
| Hypoacusis                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Eye disorders                                   |                 |                 |  |
| Cataract  |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Retinal tear                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Abdominal distension                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal pain                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 456 (0.44%) | 3 / 463 (0.65%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal pain upper                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ascites   |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                  |                 |  |
|---|------------------|-----------------|--|
| Colitis   |                  |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%)  | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Constipation                                    |                  |                 |  |
| subjects affected / exposed                     | 2 / 456 (0.44%)  | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 2 / 2            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Diarrhoea                                       |                  |                 |  |
| subjects affected / exposed                     | 11 / 456 (2.41%) | 7 / 463 (1.51%) |  |
| occurrences causally related to treatment / all | 10 / 12          | 5 / 8           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Diverticulum                                    |                  |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%)  | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Enterocolitis                                   |                  |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%)  | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Gastric haemorrhage                             |                  |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%)  | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Gastrointestinal disorder                       |                  |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%)  | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Gastrointestinal haemorrhage                    |                  |                 |  |
| subjects affected / exposed                     | 2 / 456 (0.44%)  | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 2 / 2            | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0           |  |
| Gastrointestinal polyp haemorrhage              |                  |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ileus   |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ileus paralytic                                 |                 |                 |  |
| subjects affected / exposed                     | 3 / 456 (0.66%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 3 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intestinal obstruction                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Large intestine perforation                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lower gastrointestinal haemorrhage              |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Melaena   |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nausea  |                 |                 |  |
| subjects affected / exposed                     | 3 / 456 (0.66%) | 2 / 463 (0.43%) |  |
| occurrences causally related to treatment / all | 3 / 3           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oesophagitis                                    |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Paraesthesia oral                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Small intestinal obstruction                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subileus  |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Umbilical hernia                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vomiting  |                 |                 |  |
| subjects affected / exposed                     | 2 / 456 (0.44%) | 5 / 463 (1.08%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 2 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Bile duct stone                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholecystitis acute                             |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cholelithiasis                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 456 (0.44%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatic failure                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 2 / 463 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1           |  |
| Hepatocellular injury                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Jaundice cholestatic                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Liver disorder                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Skin and subcutaneous tissue disorders          |                 |                 |  |
| Drug eruption                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Eczema  |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Erythema multiforme                             |                 |                 |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Pruritus generalised                            |                 |                  |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Purpura   |                 |                  |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Renal and urinary disorders                     |                 |                  |  |
| Acute kidney injury                             |                 |                  |  |
| subjects affected / exposed                     | 7 / 456 (1.54%) | 11 / 463 (2.38%) |  |
| occurrences causally related to treatment / all | 1 / 7           | 4 / 13           |  |
| deaths causally related to treatment / all      | 0 / 0           | 1 / 1            |  |
| Albuminuria                                     |                 |                  |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Anuria  |                 |                  |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Nephropathy                                     |                 |                  |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 1 / 463 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Nephrotic syndrome                              |                 |                  |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Proteinuria                                     |                 |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal failure                                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 5 / 463 (1.08%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal impairment                                |                 |                 |  |
| subjects affected / exposed                     | 3 / 456 (0.66%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 4           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary retention                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Endocrine disorders                             |                 |                 |  |
| Inappropriate antidiuretic hormone secretion    |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Arthralgia                                      |                 |                 |  |
| subjects affected / exposed                     | 3 / 456 (0.66%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 2 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Back pain                                       |                 |                 |  |
| subjects affected / exposed                     | 3 / 456 (0.66%) | 6 / 463 (1.30%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 0 / 6           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bone pain                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 3 / 463 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Flank pain                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Intervertebral disc protrusion                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lumbar spinal stenosis                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 2 / 463 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mobility decreased                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Muscular weakness                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 2 / 463 (0.43%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal chest pain                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal pain                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myalgia   |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteoarthritis                                  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteonecrosis of jaw                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pain in extremity                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pathological fracture                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rhabdomyolysis                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Spinal pain                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Abdominal infection                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abscess limb                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute sinusitis                                 |                 |                 |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Appendicitis                                    |                 |                  |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 2 / 463 (0.43%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Bacteraemia                                     |                 |                  |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Bacterial diarrhoea                             |                 |                  |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Bacterial infection                             |                 |                  |  |
| subjects affected / exposed                     | 2 / 456 (0.44%) | 1 / 463 (0.22%)  |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Breast abscess                                  |                 |                  |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Bronchiolitis                                   |                 |                  |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 2 / 463 (0.43%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Bronchitis                                      |                 |                  |  |
| subjects affected / exposed                     | 2 / 456 (0.44%) | 10 / 463 (2.16%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 5 / 10           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Bronchopulmonary aspergillosis                  |                 |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Bursitis infective                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Catheter site infection                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cellulitis                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 4 / 463 (0.86%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Clostridial sepsis                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Clostridium difficile infection                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Corona virus infection                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Device related infection                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 2 / 463 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 2 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diverticulitis                                  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 456 (0.00%) | 3 / 463 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Encephalomyelitis                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Enteritis infectious                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Erysipelas                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 3 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Escherichia bacteraemia                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Escherichia urinary tract infection             |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Febrile infection                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 2 / 463 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis                                 |                 |                 |  |
| subjects affected / exposed                     | 4 / 456 (0.88%) | 5 / 463 (1.08%) |  |
| occurrences causally related to treatment / all | 1 / 4           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis viral                           |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                                   | 1 / 456 (0.22%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all               | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| H1N1 influenza  |                 |                 |  |
| subjects affected / exposed                                   | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Haemophilus sepsis  |                 |                 |  |
| subjects affected / exposed                                   | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all               | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Herpes simplex encephalitis                                   |                 |                 |  |
| subjects affected / exposed                                   | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Herpes zoster   |                 |                 |  |
| subjects affected / exposed                                   | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all               | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Infection   |                 |                 |  |
| subjects affected / exposed                                   | 0 / 456 (0.00%) | 5 / 463 (1.08%) |  |
| occurrences causally related to treatment / all               | 0 / 0           | 1 / 5           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Infectious pleural effusion                                   |                 |                 |  |
| subjects affected / exposed                                   | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all               | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Infective exacerbation of chronic obstructive airways disease |                 |                 |  |
| subjects affected / exposed                                   | 1 / 456 (0.22%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all               | 1 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all                    | 0 / 0           | 0 / 0           |  |
| Influenza   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 456 (0.22%) | 3 / 463 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 2 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Listeriosis                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Localised infection                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lower respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 5 / 456 (1.10%) | 7 / 463 (1.51%) |  |
| occurrences causally related to treatment / all | 1 / 6           | 3 / 11          |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lower respiratory tract infection viral         |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lung infection                                  |                 |                 |  |
| subjects affected / exposed                     | 3 / 456 (0.66%) | 5 / 463 (1.08%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 2 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Necrotising ulcerative periodontitis            |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oral fungal infection                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteomyelitis                                   |                 |                 |  |

|   |                  |                   |  |
|---|------------------|-------------------|--|
| subjects affected / exposed                     | 0 / 456 (0.00%)  | 1 / 463 (0.22%)   |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Parainfluenzae virus infection                  |                  |                   |  |
| subjects affected / exposed                     | 0 / 456 (0.00%)  | 2 / 463 (0.43%)   |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Pharyngitis                                     |                  |                   |  |
| subjects affected / exposed                     | 1 / 456 (0.22%)  | 0 / 463 (0.00%)   |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Pneumococcal infection                          |                  |                   |  |
| subjects affected / exposed                     | 0 / 456 (0.00%)  | 1 / 463 (0.22%)   |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Pneumocystis jirovecii pneumonia                |                  |                   |  |
| subjects affected / exposed                     | 1 / 456 (0.22%)  | 0 / 463 (0.00%)   |  |
| occurrences causally related to treatment / all | 1 / 1            | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Pneumonia                                       |                  |                   |  |
| subjects affected / exposed                     | 44 / 456 (9.65%) | 49 / 463 (10.58%) |  |
| occurrences causally related to treatment / all | 16 / 52          | 16 / 55           |  |
| deaths causally related to treatment / all      | 2 / 2            | 3 / 3             |  |
| Pneumonia bacterial                             |                  |                   |  |
| subjects affected / exposed                     | 1 / 456 (0.22%)  | 1 / 463 (0.22%)   |  |
| occurrences causally related to treatment / all | 0 / 1            | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 0            | 0 / 0             |  |
| Pneumonia influenzal                            |                  |                   |  |
| subjects affected / exposed                     | 0 / 456 (0.00%)  | 2 / 463 (0.43%)   |  |
| occurrences causally related to treatment / all | 0 / 0            | 0 / 3             |  |
| deaths causally related to treatment / all      | 0 / 0            | 1 / 1             |  |
| Pneumonia moraxella                             |                  |                   |  |

|   |                 |                  |  |
|---|-----------------|------------------|--|
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Pneumonia pneumococcal                          |                 |                  |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 1 / 463 (0.22%)  |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Pseudomembranous colitis                        |                 |                  |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Pulmonary sepsis                                |                 |                  |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%)  |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0            |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0            |  |
| Pyelonephritis acute                            |                 |                  |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%)  |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Respiratory syncytial virus infection           |                 |                  |  |
| subjects affected / exposed                     | 2 / 456 (0.44%) | 0 / 463 (0.00%)  |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Respiratory tract infection                     |                 |                  |  |
| subjects affected / exposed                     | 5 / 456 (1.10%) | 10 / 463 (2.16%) |  |
| occurrences causally related to treatment / all | 2 / 5           | 3 / 11           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Respiratory tract infection viral               |                 |                  |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 2 / 463 (0.43%)  |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2            |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0            |  |
| Sepsis  |                 |                  |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 5 / 456 (1.10%) | 8 / 463 (1.73%) |  |
| occurrences causally related to treatment / all | 2 / 8           | 1 / 9           |  |
| deaths causally related to treatment / all      | 3 / 3           | 2 / 2           |  |
| Septic shock                                    |                 |                 |  |
| subjects affected / exposed                     | 3 / 456 (0.66%) | 4 / 463 (0.86%) |  |
| occurrences causally related to treatment / all | 1 / 3           | 3 / 6           |  |
| deaths causally related to treatment / all      | 2 / 2           | 3 / 3           |  |
| Sinusitis                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| 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                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tracheobronchitis                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 3 / 456 (0.66%) | 8 / 463 (1.73%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 9           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 4 / 456 (0.88%) | 8 / 463 (1.73%) |  |
| occurrences causally related to treatment / all | 1 / 5           | 3 / 9           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urosepsis                                       |                 |                 |  |
| subjects affected / exposed                     | 3 / 456 (0.66%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 1 / 1           | 0 / 0           |  |
| Viral infection                                 |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Viral upper respiratory tract infection         |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Decreased appetite                              |                 |                 |  |
| subjects affected / exposed                     | 2 / 456 (0.44%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 2 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dehydration                                     |                 |                 |  |
| subjects affected / exposed                     | 3 / 456 (0.66%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 2 / 3           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetes mellitus                               |                 |                 |  |
| subjects affected / exposed                     | 2 / 456 (0.44%) | 2 / 463 (0.43%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetes mellitus inadequate control            |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypercalcaemia                                  |                 |                 |  |
| subjects affected / exposed                     | 5 / 456 (1.10%) | 0 / 463 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 7           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperglycaemia                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 4 / 463 (0.86%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 4 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperkalaemia                                   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 456 (0.22%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoglycaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 3 / 463 (0.65%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 1 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyponatraemia                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 456 (0.22%) | 2 / 463 (0.43%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 2 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypovolaemia                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Tumour lysis syndrome                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 456 (0.00%) | 1 / 463 (0.22%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Bortezomib + DEX   | Carfilzomib + DEX  |  |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events |                    |                    |  |
| subjects affected / exposed                           | 435 / 456 (95.39%) | 446 / 463 (96.33%) |  |
| Vascular disorders                                    |                    |                    |  |
| Flushing  |                    |                    |  |
| subjects affected / exposed                           | 7 / 456 (1.54%)    | 24 / 463 (5.18%)   |  |
| occurrences (all)                                     | 13                 | 34                 |  |
| Hypertension  |                    |                    |  |
| subjects affected / exposed                           | 46 / 456 (10.09%)  | 150 / 463 (32.40%) |  |
| occurrences (all)                                     | 71                 | 356                |  |
| Hypotension   |                    |                    |  |

|   |                        |                        |  |
|---|------------------------|------------------------|--|
| subjects affected / exposed<br>occurrences (all)        | 37 / 456 (8.11%)<br>50 | 29 / 463 (6.26%)<br>36 |  |
| General disorders and administration<br>site conditions |                        |                        |  |
| Asthenia  |                        |                        |  |
| subjects affected / exposed                             | 79 / 456 (17.32%)      | 107 / 463 (23.11%)     |  |
| occurrences (all)                                       | 136                    | 231                    |  |
| Chest pain  |                        |                        |  |
| subjects affected / exposed                             | 19 / 456 (4.17%)       | 43 / 463 (9.29%)       |  |
| occurrences (all)                                       | 23                     | 54                     |  |
| Chills  |                        |                        |  |
| subjects affected / exposed                             | 12 / 456 (2.63%)       | 26 / 463 (5.62%)       |  |
| occurrences (all)                                       | 15                     | 40                     |  |
| Fatigue   |                        |                        |  |
| subjects affected / exposed                             | 140 / 456 (30.70%)     | 149 / 463 (32.18%)     |  |
| occurrences (all)                                       | 304                    | 320                    |  |
| Influenza like illness                                  |                        |                        |  |
| subjects affected / exposed                             | 10 / 456 (2.19%)       | 25 / 463 (5.40%)       |  |
| occurrences (all)                                       | 24                     | 43                     |  |
| Malaise   |                        |                        |  |
| subjects affected / exposed                             | 8 / 456 (1.75%)        | 24 / 463 (5.18%)       |  |
| occurrences (all)                                       | 8                      | 66                     |  |
| Oedema peripheral                                       |                        |                        |  |
| subjects affected / exposed                             | 77 / 456 (16.89%)      | 98 / 463 (21.17%)      |  |
| occurrences (all)                                       | 129                    | 167                    |  |
| Pyrexia   |                        |                        |  |
| subjects affected / exposed                             | 68 / 456 (14.91%)      | 145 / 463 (31.32%)     |  |
| occurrences (all)                                       | 101                    | 294                    |  |
| Respiratory, thoracic and mediastinal<br>disorders      |                        |                        |  |
| Cough   |                        |                        |  |
| subjects affected / exposed                             | 73 / 456 (16.01%)      | 127 / 463 (27.43%)     |  |
| occurrences (all)                                       | 106                    | 201                    |  |
| Dyspnoea  |                        |                        |  |
| subjects affected / exposed                             | 62 / 456 (13.60%)      | 144 / 463 (31.10%)     |  |
| occurrences (all)                                       | 87                     | 267                    |  |
| Epistaxis   |                        |                        |  |



|   |                           |                           |  |
|---|---------------------------|---------------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 14 / 456 (3.07%)<br>15    | 24 / 463 (5.18%)<br>31    |  |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)  | 19 / 456 (4.17%)<br>23    | 28 / 463 (6.05%)<br>35    |  |
| Productive cough<br>subjects affected / exposed<br>occurrences (all)  | 15 / 456 (3.29%)<br>22    | 27 / 463 (5.83%)<br>41    |  |
| Psychiatric disorders<br>Anxiety<br>subjects affected / exposed<br>occurrences (all)                            | 33 / 456 (7.24%)<br>34    | 20 / 463 (4.32%)<br>24    |  |
| Insomnia<br>subjects affected / exposed<br>occurrences (all)  | 122 / 456 (26.75%)<br>173 | 125 / 463 (27.00%)<br>236 |  |
| Investigations<br>Blood creatinine increased<br>subjects affected / exposed<br>occurrences (all)                | 30 / 456 (6.58%)<br>48    | 52 / 463 (11.23%)<br>138  |  |
| Creatinine renal clearance decreased<br>subjects affected / exposed<br>occurrences (all)                        | 19 / 456 (4.17%)<br>58    | 29 / 463 (6.26%)<br>120   |  |
| Lymphocyte count decreased<br>subjects affected / exposed<br>occurrences (all)                                  | 18 / 456 (3.95%)<br>126   | 42 / 463 (9.07%)<br>372   |  |
| Platelet count decreased<br>subjects affected / exposed<br>occurrences (all)                                    | 41 / 456 (8.99%)<br>177   | 58 / 463 (12.53%)<br>288  |  |
| Injury, poisoning and procedural complications<br>Contusion<br>subjects affected / exposed<br>occurrences (all) | 25 / 456 (5.48%)<br>29    | 20 / 463 (4.32%)<br>30    |  |
| Fall<br>subjects affected / exposed<br>occurrences (all)  | 25 / 456 (5.48%)<br>32    | 19 / 463 (4.10%)<br>32    |  |
| Nervous system disorders  |                           |                           |  |

|                                      |                    |                    |  |
|--------------------------------------|--------------------|--------------------|--|
| Dizziness                            |                    |                    |  |
| subjects affected / exposed          | 69 / 456 (15.13%)  | 42 / 463 (9.07%)   |  |
| occurrences (all)                    | 111                | 59                 |  |
| Dysgeusia                            |                    |                    |  |
| subjects affected / exposed          | 27 / 456 (5.92%)   | 17 / 463 (3.67%)   |  |
| occurrences (all)                    | 30                 | 19                 |  |
| Headache                             |                    |                    |  |
| subjects affected / exposed          | 49 / 456 (10.75%)  | 97 / 463 (20.95%)  |  |
| occurrences (all)                    | 77                 | 179                |  |
| Hypoaesthesia                        |                    |                    |  |
| subjects affected / exposed          | 14 / 456 (3.07%)   | 24 / 463 (5.18%)   |  |
| occurrences (all)                    | 21                 | 46                 |  |
| Neuralgia                            |                    |                    |  |
| subjects affected / exposed          | 72 / 456 (15.79%)  | 11 / 463 (2.38%)   |  |
| occurrences (all)                    | 123                | 23                 |  |
| Neuropathy peripheral                |                    |                    |  |
| subjects affected / exposed          | 130 / 456 (28.51%) | 49 / 463 (10.58%)  |  |
| occurrences (all)                    | 276                | 74                 |  |
| Paraesthesia                         |                    |                    |  |
| subjects affected / exposed          | 76 / 456 (16.67%)  | 43 / 463 (9.29%)   |  |
| occurrences (all)                    | 169                | 60                 |  |
| Peripheral sensory neuropathy        |                    |                    |  |
| subjects affected / exposed          | 70 / 456 (15.35%)  | 29 / 463 (6.26%)   |  |
| occurrences (all)                    | 150                | 56                 |  |
| Polyneuropathy                       |                    |                    |  |
| subjects affected / exposed          | 27 / 456 (5.92%)   | 6 / 463 (1.30%)    |  |
| occurrences (all)                    | 60                 | 7                  |  |
| Tremor                               |                    |                    |  |
| subjects affected / exposed          | 23 / 456 (5.04%)   | 10 / 463 (2.16%)   |  |
| occurrences (all)                    | 28                 | 13                 |  |
| Blood and lymphatic system disorders |                    |                    |  |
| Anaemia                              |                    |                    |  |
| subjects affected / exposed          | 131 / 456 (28.73%) | 201 / 463 (43.41%) |  |
| occurrences (all)                    | 352                | 722                |  |
| Lymphopenia                          |                    |                    |  |

|                             |                    |                    |  |
|-----------------------------|--------------------|--------------------|--|
| subjects affected / exposed | 25 / 456 (5.48%)   | 31 / 463 (6.70%)   |  |
| occurrences (all)           | 109                | 207                |  |
| Neutropenia                 |                    |                    |  |
| subjects affected / exposed | 26 / 456 (5.70%)   | 28 / 463 (6.05%)   |  |
| occurrences (all)           | 49                 | 94                 |  |
| Thrombocytopenia            |                    |                    |  |
| subjects affected / exposed | 83 / 456 (18.20%)  | 100 / 463 (21.60%) |  |
| occurrences (all)           | 241                | 483                |  |
| Eye disorders               |                    |                    |  |
| Cataract                    |                    |                    |  |
| subjects affected / exposed | 20 / 456 (4.39%)   | 36 / 463 (7.78%)   |  |
| occurrences (all)           | 25                 | 43                 |  |
| Vision blurred              |                    |                    |  |
| subjects affected / exposed | 23 / 456 (5.04%)   | 23 / 463 (4.97%)   |  |
| occurrences (all)           | 24                 | 31                 |  |
| Gastrointestinal disorders  |                    |                    |  |
| Abdominal distension        |                    |                    |  |
| subjects affected / exposed | 26 / 456 (5.70%)   | 20 / 463 (4.32%)   |  |
| occurrences (all)           | 44                 | 22                 |  |
| Abdominal pain              |                    |                    |  |
| subjects affected / exposed | 38 / 456 (8.33%)   | 32 / 463 (6.91%)   |  |
| occurrences (all)           | 58                 | 48                 |  |
| Abdominal pain upper        |                    |                    |  |
| subjects affected / exposed | 35 / 456 (7.68%)   | 24 / 463 (5.18%)   |  |
| occurrences (all)           | 50                 | 29                 |  |
| Constipation                |                    |                    |  |
| subjects affected / exposed | 127 / 456 (27.85%) | 75 / 463 (16.20%)  |  |
| occurrences (all)           | 196                | 100                |  |
| Diarrhoea                   |                    |                    |  |
| subjects affected / exposed | 184 / 456 (40.35%) | 169 / 463 (36.50%) |  |
| occurrences (all)           | 423                | 353                |  |
| Dyspepsia                   |                    |                    |  |
| subjects affected / exposed | 25 / 456 (5.48%)   | 36 / 463 (7.78%)   |  |
| occurrences (all)           | 31                 | 46                 |  |
| Nausea                      |                    |                    |  |

|   |                   |                    |  |
|---|-------------------|--------------------|--|
| subjects affected / exposed                     | 90 / 456 (19.74%) | 109 / 463 (23.54%) |  |
| occurrences (all)                               | 128               | 194                |  |
| Vomiting  |                   |                    |  |
| subjects affected / exposed                     | 45 / 456 (9.87%)  | 77 / 463 (16.63%)  |  |
| occurrences (all)                               | 62                | 157                |  |
| Skin and subcutaneous tissue disorders          |                   |                    |  |
| Pruritus  |                   |                    |  |
| subjects affected / exposed                     | 29 / 456 (6.36%)  | 34 / 463 (7.34%)   |  |
| occurrences (all)                               | 36                | 54                 |  |
| Rash  |                   |                    |  |
| subjects affected / exposed                     | 35 / 456 (7.68%)  | 42 / 463 (9.07%)   |  |
| occurrences (all)                               | 45                | 63                 |  |
| Musculoskeletal and connective tissue disorders |                   |                    |  |
| Arthralgia                                      |                   |                    |  |
| subjects affected / exposed                     | 51 / 456 (11.18%) | 61 / 463 (13.17%)  |  |
| occurrences (all)                               | 71                | 79                 |  |
| Bone pain                                       |                   |                    |  |
| subjects affected / exposed                     | 41 / 456 (8.99%)  | 50 / 463 (10.80%)  |  |
| occurrences (all)                               | 78                | 93                 |  |
| Back pain                                       |                   |                    |  |
| subjects affected / exposed                     | 81 / 456 (17.76%) | 106 / 463 (22.89%) |  |
| occurrences (all)                               | 114               | 148                |  |
| Muscle spasms                                   |                   |                    |  |
| subjects affected / exposed                     | 28 / 456 (6.14%)  | 93 / 463 (20.09%)  |  |
| occurrences (all)                               | 39                | 158                |  |
| Muscular weakness                               |                   |                    |  |
| subjects affected / exposed                     | 47 / 456 (10.31%) | 44 / 463 (9.50%)   |  |
| occurrences (all)                               | 68                | 69                 |  |
| Musculoskeletal chest pain                      |                   |                    |  |
| subjects affected / exposed                     | 20 / 456 (4.39%)  | 39 / 463 (8.42%)   |  |
| occurrences (all)                               | 25                | 51                 |  |
| Musculoskeletal pain                            |                   |                    |  |
| subjects affected / exposed                     | 25 / 456 (5.48%)  | 27 / 463 (5.83%)   |  |
| occurrences (all)                               | 29                | 33                 |  |
| Myalgia   |                   |                    |  |

|                                    |                   |                    |  |
|------------------------------------|-------------------|--------------------|--|
| subjects affected / exposed        | 19 / 456 (4.17%)  | 29 / 463 (6.26%)   |  |
| occurrences (all)                  | 34                | 39                 |  |
| Pain in extremity                  |                   |                    |  |
| subjects affected / exposed        | 50 / 456 (10.96%) | 55 / 463 (11.88%)  |  |
| occurrences (all)                  | 96                | 81                 |  |
| Infections and infestations        |                   |                    |  |
| Bronchitis                         |                   |                    |  |
| subjects affected / exposed        | 45 / 456 (9.87%)  | 103 / 463 (22.25%) |  |
| occurrences (all)                  | 78                | 162                |  |
| Conjunctivitis                     |                   |                    |  |
| subjects affected / exposed        | 37 / 456 (8.11%)  | 23 / 463 (4.97%)   |  |
| occurrences (all)                  | 49                | 30                 |  |
| Nasopharyngitis                    |                   |                    |  |
| subjects affected / exposed        | 59 / 456 (12.94%) | 79 / 463 (17.06%)  |  |
| occurrences (all)                  | 95                | 162                |  |
| Pneumonia                          |                   |                    |  |
| subjects affected / exposed        | 22 / 456 (4.82%)  | 32 / 463 (6.91%)   |  |
| occurrences (all)                  | 25                | 40                 |  |
| Respiratory tract infection        |                   |                    |  |
| subjects affected / exposed        | 32 / 456 (7.02%)  | 47 / 463 (10.15%)  |  |
| occurrences (all)                  | 45                | 92                 |  |
| Rhinitis                           |                   |                    |  |
| subjects affected / exposed        | 10 / 456 (2.19%)  | 30 / 463 (6.48%)   |  |
| occurrences (all)                  | 15                | 45                 |  |
| Upper respiratory tract infection  |                   |                    |  |
| subjects affected / exposed        | 80 / 456 (17.54%) | 117 / 463 (25.27%) |  |
| occurrences (all)                  | 135               | 247                |  |
| Urinary tract infection            |                   |                    |  |
| subjects affected / exposed        | 29 / 456 (6.36%)  | 36 / 463 (7.78%)   |  |
| occurrences (all)                  | 43                | 47                 |  |
| Metabolism and nutrition disorders |                   |                    |  |
| Decreased appetite                 |                   |                    |  |
| subjects affected / exposed        | 63 / 456 (13.82%) | 51 / 463 (11.02%)  |  |
| occurrences (all)                  | 85                | 62                 |  |
| Hyperuricaemia                     |                   |                    |  |

|                             |                   |                   |  |
|-----------------------------|-------------------|-------------------|--|
| subjects affected / exposed | 8 / 456 (1.75%)   | 31 / 463 (6.70%)  |  |
| occurrences (all)           | 11                | 58                |  |
| Hyperglycaemia              |                   |                   |  |
| subjects affected / exposed | 43 / 456 (9.43%)  | 53 / 463 (11.45%) |  |
| occurrences (all)           | 77                | 140               |  |
| Hypocalcaemia               |                   |                   |  |
| subjects affected / exposed | 19 / 456 (4.17%)  | 29 / 463 (6.26%)  |  |
| occurrences (all)           | 23                | 38                |  |
| Hypokalaemia                |                   |                   |  |
| subjects affected / exposed | 51 / 456 (11.18%) | 64 / 463 (13.82%) |  |
| occurrences (all)           | 87                | 95                |  |
| Hypophosphataemia           |                   |                   |  |
| subjects affected / exposed | 28 / 456 (6.14%)  | 33 / 463 (7.13%)  |  |
| occurrences (all)           | 56                | 74                |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment   |
|------------------|---|
| 19 December 2012 | <p>The main purpose of this amendment was to incorporate the changes from the carfilzomib Investigator's Brochure, Version 11.0 (dated 22 August 2012). Updated text of importance was included in the background information regarding relevant Phase 1 and 2 carfilzomib studies; safety and efficacy text due the carfilzomib marketing approval by the US FDA (July 2012). This amendment also included the addition of assessments for the cardiac and pulmonary substudy safety monitoring, as specified in the study objectives, as follows:</p> <ul style="list-style-type: none"><li>• Right ventricular (RV) function, RV size, RV wall thickness; and</li><li>• Pulmonary artery pressure in all subjects at baseline as well as every 12 weeks, and at the end of study for those subjects who participate in the echocardiogram substudy.</li></ul> <p>The following exploratory objectives were added:</p> <ul style="list-style-type: none"><li>• Evaluate PK/PDn relationships for safety and efficacy.</li><li>• Analyze genetic and gene expression biomarkers that may potentially predict for response and resistance following treatment with proteasome inhibitors from all subjects who consent to optional genomic biomarker analysis.</li></ul> <p>The amendment also provided administrative updates, editorial changes, and style and formatting revisions to improve clarity and consistency.</p> |
| 02 October 2014  | <p>The main purpose of this amendment was to specify that the Global Health Status/QoL Scale (measured by EORTC) subscale was to be analyzed as a secondary endpoint and that other subscales were to be analyzed as exploratory endpoints (EORTC QLQ-C30, QLQ-MY20, FACT-GOG/Ntx, and MRU). Additional major changes included the following:</p> <ul style="list-style-type: none"><li>• Added the MRD status exploratory endpoint.</li><li>• Specified the timing and details regarding bone marrow aspirate samples that were to be collected as part of the optional MRD analysis.</li><li>• Clarified procedures for survival follow-up in order to collect OS data using ad hoc survival sweeps</li><li>• Clarified that plasma concentrations of carfilzomib, along with other potential excipients, were to be determined as needed based on carfilzomib PK data analysis.</li></ul> <p>The amendment also provided administrative updates, editorial changes, and style and formatting revisions to improve clarity and consistency. There were no changes to inclusion/exclusion criteria based on this amendment.</p>  |
| 09 January 2015  | <p>The main purpose of this amendment was to specify that the number of OS events to study end was changed from 631 to 496, the number of interim analyses for OS was changed from 1 to 2, and the selected landmarks for estimating survival rate were changed from "6 months, 9 months, and 1 year" to "1 year, 2 years, and 3 years" from randomization. Additional major changes included the following:</p> <ul style="list-style-type: none"><li>• Changes in statistical analyses of secondary endpoints resulting from changes in final number of OS events were included as necessary.</li><li>• The Global Health Status/QoL subscale (measured by EORTC QLQ-C30) was moved from a secondary endpoint to an exploratory endpoint</li><li>• The FACT/GOG-Ntx questionnaire score was removed from the definition of neuropathy events and the joint model.</li></ul> <p>The amendment also provided administrative updates, editorial changes, and style and formatting revisions to improve clarity and consistency.</p>  |

|                   |   |
|-------------------|---|
| 30 October 2015   | <p>The main purpose of this amendment was to specify the following changes to the study conduct since the primary objective for this study was met:</p> <ul style="list-style-type: none"> <li>• clarified that subjects who stopped investigational product before progression were to be followed for OS</li> <li>• After the primary objective for this study was met, the following assessments were removed: central lab disease assessments and IRC review for PFS, QoL questionnaires (FACT/GOG-Ntx, EORTC QLQ-C30, QLQ-MY20, and MRU questions), and optional MRD assessments as the centralized disease assessments was removed</li> </ul> <p>Additional major changes included the following:</p> <ul style="list-style-type: none"> <li>• updated guidelines for treatment-emergent toxicities</li> <li>• updated pregnancy reporting timeframe</li> </ul>   |
| 20 September 2016 | <p>The main purpose of this amendment was to explicitly allow subjects to remain on investigational product for a minimum of 3 years or until disease progression, physician decision, unacceptable toxicity, withdrawal of consent, or mortality (whichever occurs first). The time point for completion of at least 3 years treatment and safety follow-up for all subjects who remain on treatment may occur later than the time point wherein OS reaches statistical significance or the final OS analysis occurs. Additional major changes included the following:</p> <ul style="list-style-type: none"> <li>• recommended actions for posterior reversible encephalopathy syndrome and thrombotic microangiopathy to align with the current Company Core Safety Information</li> <li>• reinserted a (non-critical) paragraph into the statistical methods and analyses section of the protocol synopsis that was mistakenly deleted during drafting of Protocol Amendment 4</li> </ul> |

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported