# Clinical trial results:
# A Randomized Controlled Study of DOXIL®/CAELYX® (doxorubicin HCL liposome injection) and VELCADE™ (bortezomib) or VELCADE Monotherapy for the Treatment of Relapsed Multiple Myeloma

Due to a system error, the data reported in v1 is not correct and has been removed from public view.

## Summary

| | |
|---|---|
| EudraCT number | 2004-001842-34 |
| Trial protocol | AT CZ GB ES IT |
| Global end of trial date | 05 June 2014 |

**Results information**

| | |
|---|---|
| Result version number | v2 (current) |
| This version publication date | 01 July 2016 |
| First version publication date | 06 August 2015 |
| Version creation reason | • Correction of full data set<br>Review of data |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | DOXIL-MMY-3001 |

**Additional study identifiers**

| | |
|---|---|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00103506 |
| WHO universal trial number (UTN) | - |

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Johnson & Johnson Pharmaceutical Research and Development |
| Sponsor organisation address | Berkeley, California, United States, |
| Public contact | Clinical Registry Group, Johnson & Johnson Pharmaceutical Research and Development, ClinicalTrialsEU@its.jnj.com |
| Scientific contact | Clinical Registry Group, Johnson & Johnson Pharmaceutical Research and Development, ClinicalTrialsEU@its.jnj.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 June 2014 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 05 June 2014 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study is to test the hypothesis that treatment with DOXIL/CAELYX and VELCADE in combination, will result in a longer time to progression (TTP) than VELCADE monotherapy in subjects with relapsed multiple myeloma.

Protection of trial subjects:

The safety assessments included, clinical laboratory results, tests for cardiac function (multiple-gated acquisition scan/echocardiogram and electrocardiogram) and adverse events were monitored throughout the study.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 20 December 2004 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety |
| Long term follow-up duration | 8 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Argentina: 15 |
| Country: Number of subjects enrolled | Australia: 62 |
| Country: Number of subjects enrolled | Austria: 18 |
| Country: Number of subjects enrolled | Belgium: 20 |
| Country: Number of subjects enrolled | Canada: 43 |
| Country: Number of subjects enrolled | Czech Republic: 36 |
| Country: Number of subjects enrolled | France: 49 |
| Country: Number of subjects enrolled | Israel: 46 |
| Country: Number of subjects enrolled | Italy: 28 |
| Country: Number of subjects enrolled | Netherlands: 61 |
| Country: Number of subjects enrolled | Poland: 52 |
| Country: Number of subjects enrolled | Portugal: 20 |
| Country: Number of subjects enrolled | Russian Federation: 72 |
| Country: Number of subjects enrolled | Singapore: 5 |
| Country: Number of subjects enrolled | South Africa: 28 |
| Country: Number of subjects enrolled | Spain: 35 |
| Country: Number of subjects enrolled | United Kingdom: 15 |

| | |
|---|---|
| Country: Number of subjects enrolled | United States: 41 |
| Worldwide total number of subjects | 646 |
| EEA total number of subjects | 334 |

Notes:

**Subjects enrolled per age group**

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 0 |
| Children (2-11 years) | 0 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 396 |
| From 65 to 84 years | 247 |
| 85 years and over | 3 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

A total of 646 participants were enrolled into the study, with 324 subjects randomized to receive DOXIL/CAELYX and VELCADE combination therapy and 322 participants randomized to receive VELCADE monotherapy.

### 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 |
| **Arm title** | Velcade (Bortezomib) Monotherapy |

Arm description:

Velcade (bortezomib) 1.3 milligram/meter per square (mg/m^2) by rapid (bolus) intravenous (IV) administration given on Day 1, 4, 8, and 11 of each 21-day cycle for up to 8 cycles.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Bortezomib |
| Investigational medicinal product code | PS-341 |
| Other name | VELCADE |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Participants were administered 1.3 milligram (mg) of Bortezomib by rapid bolus intravenous (i.v.) administration given on Days 1, 4, 8, and 11 of each 21-day cycle for up to 8 cycles

| | |
|---|---|
| **Arm title** | Doxil/Caelyx Plus Velcade (Bortezomib) |

Arm description:

Velcade (bortezomib) 1.3 milligram per meter square (mg/m^2) by rapid (bolus) IV administration given on Day 1, 4, 8, and 11 of each 21-day cycle for up to 8 cycles. Doxorubicin hydrochloride (DOXIL/CAELYX) 30 mg/m^2 by IV infusion will be given on Day 4 of every 21-day cycle after the administration of VELCADE (bortezomib) up to 8 cycles.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Bortezomib |
| Investigational medicinal product code | PS-341 |
| Other name | VELCADE |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Participants were administered 1.3 milligram (mg) of Bortezomib by rapid bolus intravenous (i.v.) administration given on Days 1, 4, 8, and 11 of each 21-day cycle for up to 8 cycles

| | |
|---|---|
| Investigational medicinal product name | Doxorubicin hydrochloride |
| Investigational medicinal product code | Doxorubicin HCL Liposome Injection |
| Other name | DOXIL/CAELYX |
| Pharmaceutical forms | Solution for infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

Participants were administered  Doxorubicin hydrochloride (DOXIL/CAELYX) 30 milligram per metere

sqaure (mg/m2)  by intravenous (i.v) infusion on Day 4 of every 21-day cycle after the administration of bortezomib (VELCADE) for up to 8 cycles.

| **Number of subjects in period 1** | Velcade (Bortezomib) Monotherapy | Doxil/Caelyx Plus Velcade (Bortezomib) |
|---|---|---|
| Started | 322 | 324 |
| Completed | 0 | 0 |
| Not completed | 322 | 324 |
| Consent withdrawn by subject | 13 | 24 |
| Physician decision | 6 | 9 |
| Adverse event, non-fatal | 81 | 105 |
| Other | 218 | 181 |
| Adverse event, serious non-fatal | 2 | 5 |
| Lost to follow-up | 2 | - |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | Velcade (Bortezomib) Monotherapy |
| Reporting group description: | |
| Velcade (bortezomib) 1.3 milligram/meter per square (mg/m^2) by rapid (bolus) intravenous (IV) administration given on Day 1, 4, 8, and 11 of each 21-day cycle for up to 8 cycles. | |
| Reporting group title | Doxil/Caelyx Plus Velcade (Bortezomib) |
| Reporting group description: | |
| Velcade (bortezomib) 1.3 milligram per meter square (mg/m^2) by rapid (bolus) IV administration given on Day 1, 4, 8, and 11 of each 21-day cycle for up to 8 cycles. Doxorubicin hydrochloride (DOXIL/CAELYX) 30 mg/m^2 by IV infusion will be given on Day 4 of every 21-day cycle after the administration of VELCADE (bortezomib) up to 8 cycles. | |

| Reporting group values | Velcade (Bortezomib) Monotherapy | Doxil/Caelyx Plus Velcade (Bortezomib) | Total |
|---|---|---|---|
| Number of subjects | 322 | 324 | 646 |
| Title for AgeCategorical<br>Units: subjects | | | |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 193 | 203 | 396 |
| From 65 to 84 years | 127 | 120 | 247 |
| 85 years and over | 2 | 1 | 3 |
| Title for AgeContinuous<br>Units: years | | | |
| arithmetic mean | 61.5 | 61.4 | |
| standard deviation | ± 9.56 | ± 9.61 | - |
| Title for Gender<br>Units: subjects | | | |
| Female | 148 | 135 | 283 |
| Male | 174 | 189 | 363 |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | Velcade (Bortezomib) Monotherapy |
| Reporting group description: | |
| Velcade (bortezomib) 1.3 milligram/meter per square (mg/m^2) by rapid (bolus) intravenous (IV) administration given on Day 1, 4, 8, and 11 of each 21-day cycle for up to 8 cycles. | |
| Reporting group title | Doxil/Caelyx Plus Velcade (Bortezomib) |
| Reporting group description: | |
| Velcade (bortezomib) 1.3 milligram per meter square (mg/m^2) by rapid (bolus) IV administration given on Day 1, 4, 8, and 11 of each 21-day cycle for up to 8 cycles. Doxorubicin hydrochloride (DOXIL/CAELYX) 30 mg/m^2 by IV infusion will be given on Day 4 of every 21-day cycle after the administration of VELCADE (bortezomib) up to 8 cycles. | |

### Primary: Time to Progression (TTP)

| | |
|---|---|
| End point title | Time to Progression (TTP)[1] |
| End point description: | |
| Median time to progression of disease is assessed according to International Myeloma Working Group (IMWG) criteria or death from any cause. IMWG criteria: increase of less than or equal (>=) 25% from lowest level in Serum M-component or (the absolute increase must be >=0.5 gram per deciliter [g/dL]); Urine M component or (the absolute increase must be >=200 milligram per 24 hour. Only in participants without measurable serum and urine M-protein levels: the difference between involved and uninvolved free light chain levels. The absolute increase >10 mg/dL. Bone marrow plasma cell percentage >=10%. Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing. Development of hypercalcemia. Participants who died or dropped out due to any reason without progression will be censored with the day of death or drop-out, respectively and who are alive at the end of the study without any progression was censored with the last available date. | |
| End point type | Primary |
| End point timeframe: | |
| From date of first participant randomization (20 December 2004) up to interim analysis cut-off date (28 April 2006). | |
| Notes: | |
| [1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.<br>Justification: Descriptive statistics were done, no inferential statistical analyses were performed | |

| End point values | Velcade (Bortezomib) Monotherapy | Doxil/Caelyx Plus Velcade (Bortezomib) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 322 | 324 | | |
| Units: Months | | | | |
| median (full range (min-max)) | 6.5 (5.6 to 7.1) | 9.3 (8.2 to 11.1) | | |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Overall Survival

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

End point description:

The overall survival is defined as the time from the date of first dose of study drug to date of death from any cause. If the participant is alive or the vital status is unknown, the participant will be censored at the date the participant will be last known to be alive.

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

End point timeframe:

From date of first participant randomization (20 December 2004) to cut-off date for final survival analysis (16 May 2014).

| **End point values** | Velcade (Bortezomib) Monotherapy | Doxil/Caelyx Plus Velcade (Bortezomib) | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 322 | 324 | | |
| Units: months | | | | |
| median (full range (min-max)) | 30.8 (25.2 to 36.5) | 33 (28.9 to 37.1) | | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: Day 1 to follow up | |
| Assessment type | Non-systematic |
| **Dictionary used** | |
| Dictionary name | MedDRA |
| Dictionary version | 9.0 |
| **Reporting groups** | |
| Reporting group title | VELCADE |
| Reporting group description: bortezomib monotherapy | |
| Reporting group title | DOXIL + VELCADE |
| Reporting group description: doxorubicin hydrochloride [HCl] liposome injection and bortezomib combination therapy | |

| Serious adverse events | VELCADE | DOXIL + VELCADE | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 105 / 322 (32.61%) | 120 / 324 (37.04%) | |
| number of deaths (all causes) | 12 | 12 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Cancer Pain | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Tumour Lysis Syndrome | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Colon Cancer | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Deep Vein Thrombosis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 4 / 324 (1.23%) | |
| occurrences causally related to treatment / all | 2 / 2 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Phlebitis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Orthostatic Hypotension | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombophlebitis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Catheter Related Complication | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest Pain | | | |
| subjects affected / exposed | 3 / 322 (0.93%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Chills | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 3 / 324 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Hyperthermia | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General Physical Health Deterioration | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza Like Illness | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oedema Peripheral | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multi-Organ Failure | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 8 / 322 (2.48%) | 15 / 324 (4.63%) | |
| occurrences causally related to treatment / all | 5 / 8 | 14 / 17 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sudden Cardiac Death | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Sudden Death | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast disorders | | | |
| Benign Prostatic Hyperplasia | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epididymitis | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute Pulmonary Oedema | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 322 (0.31%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Chronic Obstructive Pulmonary Disease | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 6 / 322 (1.86%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 5 / 6 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea Exertional | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Interstitial Lung Disease | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary Embolism | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Pulmonary Fibrosis | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Pulmonary Hypertension | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 322 (0.00%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Pulmonary Oedema | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory Failure | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Psychiatric disorders | | | |
| Agitation | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anxiety | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Completed Suicide | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Nervousness | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Suicidal Ideation | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |

| | | | |
|---|---|---|---|
| Blood Creatinine Increased | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 3 / 324 (0.93%) | |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood Glucose Increased | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Troponin I Increased | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ejection Fraction Decreased | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Drug Toxicity | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Fall | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skeletal Injury | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal Compression Fracture | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|---|---|---|
| Thoracic Vertebral Fracture | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute Myocardial Infarction | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina Pectoris | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina Unstable | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial Fibrillation | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arrhythmia | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial Flutter | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac Arrest | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Cardiac Failure | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 322 (0.62%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac Failure Chronic | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac Failure Congestive | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 1 / 2 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardio-Respiratory Arrest | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial Infarction | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nodal Arrhythmia | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Right Ventricular Failure | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tachyarrhythmia | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Autonomic Neuropathy | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cauda Equina Syndrome | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Balance Disorder | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral Haemorrhage | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral Ischaemia | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral Infarction | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coordination Abnormal | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar Radiculopathy | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuralgia | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuropathy Peripheral | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neuropathy | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paralysis | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paraparesis | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (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 | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Polyneuropathy | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Quadriparesis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Polyneuropathy in Malignant Disease | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal Cord Compression | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 3 / 324 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tremor | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 4 / 322 (1.24%) | 4 / 324 (1.23%) | |
| occurrences causally related to treatment / all | 4 / 5 | 3 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| **Blood and lymphatic system disorders** | | | |
| Anaemia | | | |
| subjects affected / exposed | 4 / 322 (1.24%) | 3 / 324 (0.93%) | |
| occurrences causally related to treatment / all | 2 / 4 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile Neutropenia | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 5 / 324 (1.54%) | |
| occurrences causally related to treatment / all | 0 / 3 | 11 / 12 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 322 (0.00%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 9 / 324 (2.78%) | |
| occurrences causally related to treatment / all | 0 / 0 | 9 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancytopenia | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Deafness | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vertigo | | | |
| subjects affected / exposed | 3 / 322 (0.93%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Corneal Erosion | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diplopia | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinal Vein Thrombosis | | | |

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|---|---|---|---|
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (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 Pain | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 1 / 2 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 6 / 322 (1.86%) | 7 / 324 (2.16%) | |
| occurrences causally related to treatment / all | 7 / 8 | 8 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspepsia | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dysphagia | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Faecaloma | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Flatulence | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric Ulcer | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroduodenal Haemorrhage | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Gastrointestinal Haemorrhage | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 3 / 324 (0.93%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrooesophageal Reflux Disease | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematemesis | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 2 / 2 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus Paralytic | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Large Intestine Perforation | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mallory-Weiss Syndrome | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nausea | | | |

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|---|---|---|---|
| subjects affected / exposed | 3 / 322 (0.93%) | 7 / 324 (2.16%) | |
| occurrences causally related to treatment / all | 3 / 3 | 6 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal Haemorrhage | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rectal Prolapse | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Small Intestinal Obstruction | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper Gastrointestinal Haemorrhage | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Stomatitis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 13 / 324 (4.01%) | |
| occurrences causally related to treatment / all | 1 / 2 | 15 / 15 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Epidermal Necrosis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Palmar-Plantar Erythrodysaesthesia Syndrome | | | |

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|---|---|---|---|
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Jessner's Lymphocytic Infiltration | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Swelling Face | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Calculus Bladder | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematuria | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephritis Interstitial | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal Colic | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| 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 | 2 / 322 (0.62%) | 3 / 324 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Renal Failure Acute | | | |
| subjects affected / exposed | 5 / 322 (1.55%) | 4 / 324 (1.23%) | |
| occurrences causally related to treatment / all | 5 / 6 | 4 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Renal Failure Chronic | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal Impairment | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary Bladder Haemorrhage | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary Retention | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Adrenal Insufficiency | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercorticoidism | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Inappropriate Antidiuretic Hormone Secretion | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (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 | 2 / 322 (0.62%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone Lesion | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back Pain | | | |
| subjects affected / exposed | 3 / 322 (0.93%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone Pain | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bursitis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Joint Instability | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myalgia | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal Chest Pain | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteonecrosis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pain in Extremity | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pathological Fracture | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Abdominal Infection | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacterial Sepsis | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis Acute | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis Chronic | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 2 / 322 (0.62%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Candidiasis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchopneumonia | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 3 / 324 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Catheter Related Infection | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea Infectious | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear Infection | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Furuncle | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 3 / 322 (0.93%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 3 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes Zoster | | | |
| subjects affected / exposed | 3 / 322 (0.93%) | 5 / 324 (1.54%) | |
| occurrences causally related to treatment / all | 2 / 3 | 5 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Genitourinary Tract Infection | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes Zoster Disseminated | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Klebsiella Sepsis | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Laryngitis | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (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 | 3 / 322 (0.93%) | 3 / 324 (0.93%) | |
| occurrences causally related to treatment / all | 2 / 3 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lobar Pneumonia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningitis Bacterial | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Opportunistic Infection | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic Sepsis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Orchitis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteomyelitis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumococcal Bacteraemia | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumococcal Sepsis | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumocystis JiroveCI Pneumonia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 20 / 322 (6.21%) | 16 / 324 (4.94%) | |
| occurrences causally related to treatment / all | 13 / 21 | 11 / 17 | |
| deaths causally related to treatment / all | 3 / 4 | 1 / 3 | |
| Pneumonia Aspergillus | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia Legionella | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pseudomonas Infection | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia Pneumococcal | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory Tract Infection | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 3 / 324 (0.93%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Respiratory Tract Infection Bacterial | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic Embolus | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic Shock | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 3 / 324 (0.93%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Sinusitis | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin Infection | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal Sepsis | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper Respiratory Tract Infection | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 4 / 324 (1.23%) | |
| occurrences causally related to treatment / all | 1 / 3 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary Tract Infection | | | |
| subjects affected / exposed | 2 / 322 (0.62%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Anorexia | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 2 / 324 (0.62%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 6 / 322 (1.86%) | 6 / 324 (1.85%) | |
| occurrences causally related to treatment / all | 5 / 8 | 6 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gout | | | |
| subjects affected / exposed | 0 / 322 (0.00%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 0 / 324 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 322 (0.31%) | 1 / 324 (0.31%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 3 / 324 (0.93%) | |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| **Non-serious adverse events** | VELCADE | DOXIL + VELCADE | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 298 / 322 (92.55%) | 313 / 324 (96.60%) | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 17 / 322 (5.28%) | 15 / 324 (4.63%) | |
| occurrences (all) | 18 | 22 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 56 / 322 (17.39%) | 70 / 324 (21.60%) | |
| occurrences (all) | 84 | 138 | |
| Fatigue | | | |
| subjects affected / exposed | 88 / 322 (27.33%) | 115 / 324 (35.49%) | |
| occurrences (all) | 157 | 220 | |
| Chills | | | |
| subjects affected / exposed | 18 / 322 (5.59%) | 25 / 324 (7.72%) | |
| occurrences (all) | 19 | 44 | |
| Influenza Like Illness | | | |
| subjects affected / exposed | 13 / 322 (4.04%) | 18 / 324 (5.56%) | |
| occurrences (all) | 14 | 36 | |
| Oedema Peripheral | | | |
| subjects affected / exposed | 27 / 322 (8.39%) | 32 / 324 (9.88%) | |
| occurrences (all) | 34 | 38 | |
| Pyrexia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 67 / 322 (20.81%) | 91 / 324 (28.09%) | |
| occurrences (all) | 124 | 154 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 38 / 322 (11.80%) | 58 / 324 (17.90%) | |
| occurrences (all) | 48 | 69 | |
| Dyspnoea | | | |
| subjects affected / exposed | 22 / 322 (6.83%) | 32 / 324 (9.88%) | |
| occurrences (all) | 35 | 40 | |
| Epistaxis | | | |
| subjects affected / exposed | 12 / 322 (3.73%) | 18 / 324 (5.56%) | |
| occurrences (all) | 12 | 22 | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 43 / 322 (13.35%) | 35 / 324 (10.80%) | |
| occurrences (all) | 45 | 43 | |
| Investigations | | | |
| Weight Decreased | | | |
| subjects affected / exposed | 12 / 322 (3.73%) | 37 / 324 (11.42%) | |
| occurrences (all) | 15 | 43 | |
| Nervous system disorders | | | |
| Dysgeusia | | | |
| subjects affected / exposed | 9 / 322 (2.80%) | 18 / 324 (5.56%) | |
| occurrences (all) | 9 | 23 | |
| Dizziness | | | |
| subjects affected / exposed | 27 / 322 (8.39%) | 32 / 324 (9.88%) | |
| occurrences (all) | 43 | 45 | |
| Headache | | | |
| subjects affected / exposed | 56 / 322 (17.39%) | 59 / 324 (18.21%) | |
| occurrences (all) | 84 | 89 | |
| Neuropathy | | | |
| subjects affected / exposed | 38 / 322 (11.80%) | 35 / 324 (10.80%) | |
| occurrences (all) | 53 | 48 | |
| Neuralgia | | | |
| subjects affected / exposed | 63 / 322 (19.57%) | 54 / 324 (16.67%) | |
| occurrences (all) | 113 | 88 | |

| | | | |
|---|---|---|---|
| Neuropathy Peripheral | | | |
| subjects affected / exposed | 46 / 322 (14.29%) | 36 / 324 (11.11%) | |
| occurrences (all) | 77 | 60 | |
| Paraesthesia | | | |
| subjects affected / exposed | 31 / 322 (9.63%) | 41 / 324 (12.65%) | |
| occurrences (all) | 41 | 57 | |
| Peripheral Sensory Neuropathy | | | |
| subjects affected / exposed | 42 / 322 (13.04%) | 41 / 324 (12.65%) | |
| occurrences (all) | 83 | 69 | |
| Polyneuropathy | | | |
| subjects affected / exposed | 27 / 322 (8.39%) | 26 / 324 (8.02%) | |
| occurrences (all) | 56 | 63 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 67 / 322 (20.81%) | 80 / 324 (24.69%) | |
| occurrences (all) | 170 | 236 | |
| Leukopenia | | | |
| subjects affected / exposed | 23 / 322 (7.14%) | 28 / 324 (8.64%) | |
| occurrences (all) | 95 | 152 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 89 / 322 (27.64%) | 104 / 324 (32.10%) | |
| occurrences (all) | 379 | 488 | |
| Neutropenia | | | |
| subjects affected / exposed | 71 / 322 (22.05%) | 113 / 324 (34.88%) | |
| occurrences (all) | 270 | 510 | |
| Eye disorders | | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 17 / 322 (5.28%) | 24 / 324 (7.41%) | |
| occurrences (all) | 21 | 28 | |
| Gastrointestinal disorders | | | |
| Abdominal Pain | | | |
| subjects affected / exposed | 23 / 322 (7.14%) | 32 / 324 (9.88%) | |
| occurrences (all) | 24 | 41 | |
| Abdominal Pain Upper | | | |
| subjects affected / exposed | 13 / 322 (4.04%) | 24 / 324 (7.41%) | |
| occurrences (all) | 14 | 32 | |
| Constipation | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 98 / 322 (30.43%) | 99 / 324 (30.56%) | |
| occurrences (all) | 132 | 141 | |
| Dyspepsia | | | |
| subjects affected / exposed | 13 / 322 (4.04%) | 27 / 324 (8.33%) | |
| occurrences (all) | 15 | 39 | |
| Diarrhoea | | | |
| subjects affected / exposed | 122 / 322 (37.89%) | 142 / 324 (43.83%) | |
| occurrences (all) | 237 | 295 | |
| Nausea | | | |
| subjects affected / exposed | 125 / 322 (38.82%) | 152 / 324 (46.91%) | |
| occurrences (all) | 231 | 303 | |
| Stomatitis | | | |
| subjects affected / exposed | 11 / 322 (3.42%) | 55 / 324 (16.98%) | |
| occurrences (all) | 12 | 75 | |
| Vomiting | | | |
| subjects affected / exposed | 67 / 322 (20.81%) | 93 / 324 (28.70%) | |
| occurrences (all) | 106 | 166 | |
| Skin and subcutaneous tissue disorders | | | |
| Dry Skin | | | |
| subjects affected / exposed | 7 / 322 (2.17%) | 28 / 324 (8.64%) | |
| occurrences (all) | 7 | 30 | |
| Palmar-Plantar Erythrodysaesthesia Syndrome | | | |
| subjects affected / exposed | 1 / 322 (0.31%) | 62 / 324 (19.14%) | |
| occurrences (all) | 1 | 114 | |
| Pruritus | | | |
| subjects affected / exposed | 16 / 322 (4.97%) | 20 / 324 (6.17%) | |
| occurrences (all) | 25 | 25 | |
| Rash | | | |
| subjects affected / exposed | 29 / 322 (9.01%) | 48 / 324 (14.81%) | |
| occurrences (all) | 45 | 69 | |
| Musculoskeletal and connective tissue disorders | | | |
| Back Pain | | | |
| subjects affected / exposed | 37 / 322 (11.49%) | 38 / 324 (11.73%) | |
| occurrences (all) | 49 | 43 | |
| Arthralgia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 27 / 322 (8.39%) | 34 / 324 (10.49%) | |
| occurrences (all) | 36 | 50 | |
| Bone Pain | | | |
| subjects affected / exposed | 25 / 322 (7.76%) | 10 / 324 (3.09%) | |
| occurrences (all) | 36 | 10 | |
| Musculoskeletal Chest Pain | | | |
| subjects affected / exposed | 12 / 322 (3.73%) | 20 / 324 (6.17%) | |
| occurrences (all) | 12 | 24 | |
| Pain in Extremity | | | |
| subjects affected / exposed | 47 / 322 (14.60%) | 34 / 324 (10.49%) | |
| occurrences (all) | 66 | 40 | |
| Myalgia | | | |
| subjects affected / exposed | 20 / 322 (6.21%) | 10 / 324 (3.09%) | |
| occurrences (all) | 27 | 10 | |
| Infections and infestations | | | |
| Herpes Zoster | | | |
| subjects affected / exposed | 26 / 322 (8.07%) | 30 / 324 (9.26%) | |
| occurrences (all) | 28 | 32 | |
| Bronchitis | | | |
| subjects affected / exposed | 14 / 322 (4.35%) | 25 / 324 (7.72%) | |
| occurrences (all) | 15 | 32 | |
| Herpes Simplex | | | |
| subjects affected / exposed | 18 / 322 (5.59%) | 32 / 324 (9.88%) | |
| occurrences (all) | 19 | 39 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 20 / 322 (6.21%) | 25 / 324 (7.72%) | |
| occurrences (all) | 23 | 31 | |
| Pneumonia | | | |
| subjects affected / exposed | 9 / 322 (2.80%) | 18 / 324 (5.56%) | |
| occurrences (all) | 11 | 20 | |
| Upper Respiratory Tract Infection | | | |
| subjects affected / exposed | 32 / 322 (9.94%) | 30 / 324 (9.26%) | |
| occurrences (all) | 46 | 52 | |
| Metabolism and nutrition disorders | | | |
| Anorexia | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 43 / 322 (13.35%) | 58 / 324 (17.90%) | |
| occurrences (all) | 63 | 99 | |
| Decreased Appetite | | | |
| subjects affected / exposed | 9 / 322 (2.80%) | 30 / 324 (9.26%) | |
| occurrences (all) | 13 | 39 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 9 / 322 (2.80%) | 19 / 324 (5.86%) | |
| occurrences (all) | 11 | 32 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 12 / 322 (3.73%) | 17 / 324 (5.25%) | |
| occurrences (all) | 21 | 35 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 15 / 322 (4.66%) | 23 / 324 (7.10%) | |
| occurrences (all) | 22 | 31 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 20 September 2006 | After the protocol-specified interim analysis, the Independent Data Monitoring Committee (IDMC) concluded that there was a significant benefit to subjects randomized to receive DOXIL/CAELYX and VELCADE regarding the primary endpoint, time to progression, as well as progression - free survival. While there was an increase in adverse events associated with the combination therapy, this increase was judged to be acceptable in the context of the benefits. The primary objective of this amendment is to communicate this result to the investigators, who can then offer the subjects who were randomized to VELCADE monotherapy and are still actively receiving study treatment the option to cross over to receive the combination therapy. |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

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

Study stopped in terms of primary endpoint based on its results at planned interim analysis (28 Apr 2006). However, Long-term follow-up for survival continued until 2014.

Notes: