



Clinical trial results: An International, Multicenter, Randomized, Double-Blind Study of Vorinostat (MK-0683) or Placebo in Combination with Bortezomib in Patients with Multiple Myeloma

Summary

| | |
|--------------------------|-------------------------------------|
| EudraCT number | 2008-003752-30 |
| Trial protocol | ES DE BE FR AT CZ PT HU IT BG GB GR |
| Global end of trial date | 30 June 2015 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 24 June 2016 |
| First version publication date | 24 June 2016 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 0683-088 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|--|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00773747 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Merck Registration Number: MK-0683-088 |

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|-------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 30 June 2015 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 08 September 2011 |
| Global end of trial reached? | Yes |
| Global end of trial date | 30 June 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

This was a multi-site, randomized, double-blind study to determine the safety and efficacy of vorinostat (MK-0683/Zolinza®) and bortezomib compared with placebo and bortezomib in participants with relapsed or refractory multiple myeloma. The primary measurement of efficacy was the duration of progression-free survival.

Protection of trial subjects:

This study was conducted in conformance with Good Clinical Practice standards and applicable country and/or local statutes and regulations regarding ethical committee review, informed consent, and the protection of human subjects participating in biomedical research. Study-specific patient protections include implementation of a stopping rule for futility, stopping rule for overwhelming efficacy, and dose modification based on worst severity toxicities experienced by participants.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 01 December 2008 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United States: 29 |
| Country: Number of subjects enrolled | Australia: 38 |
| Country: Number of subjects enrolled | Argentina: 1 |
| Country: Number of subjects enrolled | Austria: 8 |
| Country: Number of subjects enrolled | Belgium: 11 |
| Country: Number of subjects enrolled | Brazil: 29 |
| Country: Number of subjects enrolled | Bulgaria: 35 |
| Country: Number of subjects enrolled | Canada: 16 |
| Country: Number of subjects enrolled | China: 81 |
| Country: Number of subjects enrolled | Croatia: 13 |
| Country: Number of subjects enrolled | Czech Republic: 33 |
| Country: Number of subjects enrolled | France: 13 |
| Country: Number of subjects enrolled | Germany: 15 |
| Country: Number of subjects enrolled | Greece: 23 |
| Country: Number of subjects enrolled | Hong Kong: 6 |
| Country: Number of subjects enrolled | Hungary: 2 |
| Country: Number of subjects enrolled | India: 48 |

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Israel: 1 |
| Country: Number of subjects enrolled | Italy: 11 |
| Country: Number of subjects enrolled | Korea, Republic of: 38 |
| Country: Number of subjects enrolled | Malaysia: 8 |
| Country: Number of subjects enrolled | Mexico: 4 |
| Country: Number of subjects enrolled | New Zealand: 35 |
| Country: Number of subjects enrolled | Philippines: 28 |
| Country: Number of subjects enrolled | Poland: 12 |
| Country: Number of subjects enrolled | Portugal: 7 |
| Country: Number of subjects enrolled | Romania: 10 |
| Country: Number of subjects enrolled | Russian Federation: 7 |
| Country: Number of subjects enrolled | South Africa: 19 |
| Country: Number of subjects enrolled | Spain: 20 |
| Country: Number of subjects enrolled | Taiwan: 11 |
| Country: Number of subjects enrolled | Thailand: 14 |
| Country: Number of subjects enrolled | United Kingdom: 11 |
| Worldwide total number of subjects | 637 |
| EEA total number of subjects | 224 |

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) | 381 |
| From 65 to 84 years | 253 |
| 85 years and over | 3 |

Subject disposition

Recruitment

Recruitment details:

This study enrolled participants with an established diagnosis of multiple myeloma based on standard criteria that have received at least 1 but not more than 3 prior anti-myeloma regimens and have demonstrated progressive disease after the most recent treatment regimen. Additional inclusion and exclusion criteria applied.

Pre-assignment

Screening details:

637 participants were randomized to treatment and 635 participants received at least 1 dose of MK-0683 or placebo: 315 participants were treated with vorinostat + bortezomib and 320 participants were treated with placebo + bortezomib.

Period 1

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

Arms

| | |
|------------------------------|-------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Vorinostat + Bortezomib |

Arm description:

Participants will receive vorinostat four 100 mg capsules (400 mg total) orally 0-30 minutes after a meal on Days 1 through 14 of a 21-day treatment cycle and bortezomib 1.3 mg/m² by intravenous injection on Days 1, 4, 8, and 11 of a 21-day treatment cycle.

| | |
|--|-------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Vorinostat 400 mg |
| Investigational medicinal product code | |
| Other name | ZOLINZA® |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Vorinostat 400 mg orally 0-30 minutes after a meal on Days 1 through 14 of a 21-day treatment cycle

| | |
|--|-----------------------------------|
| Investigational medicinal product name | Bortezomib 1.3 mg/m ² |
| Investigational medicinal product code | |
| Other name | VELCADE® |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Bortezomib 1.3 mg/m² by intravenous injection on Days 1, 4, 8, and 11 Of a 21-day treatment cycle

| | |
|------------------|----------------------|
| Arm title | Placebo + Bortezomib |
|------------------|----------------------|

Arm description:

Participants will receive four placebo capsules orally 0-30 minutes after a meal on Days 1 through 14 of a 21-day treatment cycle and bortezomib 1.3 mg/m² by intravenous injection on Days 1, 4, 8, and 11 Of a 21-day treatment cycle.

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

| | |
|--|-----------------------------------|
| Investigational medicinal product name | Bortezomib 1.3 mg/m ² |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Intravenous use |

Dosage and administration details:

Bortezomib 1.3 mg/m² by intravenous injection on Days 1, 4, 8, and 11 Of a 21-day treatment cycle

| | |
|--|---------------------------------|
| Investigational medicinal product name | Matching Placebo for Vorinostat |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Placebo capsules orally 0-30 minutes after a meal on Days 1 through 14 of a 21-day treatment cycle

| Number of subjects in period 1 | Vorinostat + Bortezomib | Placebo + Bortezomib |
|---------------------------------------|-------------------------|----------------------|
| Started | 317 | 320 |
| Completed | 22 | 24 |
| Not completed | 295 | 296 |
| Adverse event, serious fatal | 5 | 8 |
| Consent withdrawn by subject | 89 | 61 |
| Physician decision | 26 | 18 |
| Adverse event, non-fatal | 61 | 62 |
| Lost to follow-up | - | 1 |
| Lack of efficacy | 112 | 144 |
| Protocol deviation | 2 | 2 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------------------|
| Reporting group title | Vorinostat + Bortezomib |
|-----------------------|-------------------------|

Reporting group description:

Participants will receive vorinostat four 100 mg capsules (400 mg total) orally 0-30 minutes after a meal on Days 1 through 14 of a 21-day treatment cycle and bortezomib 1.3 mg/m² by intravenous injection on Days 1, 4, 8, and 11 of a 21-day treatment cycle.

| | |
|-----------------------|----------------------|
| Reporting group title | Placebo + Bortezomib |
|-----------------------|----------------------|

Reporting group description:

Participants will receive four placebo capsules orally 0-30 minutes after a meal on Days 1 through 14 of a 21-day treatment cycle and bortezomib 1.3 mg/m² by intravenous injection on Days 1, 4, 8, and 11 Of a 21-day treatment cycle.

| Reporting group values | Vorinostat + Bortezomib | Placebo + Bortezomib | Total |
|--|-------------------------|----------------------|-------|
| Number of subjects | 317 | 320 | 637 |
| Age Categorical | | | |
| Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 200 | 181 | 381 |
| From 65-84 years | 116 | 137 | 253 |
| 85 years and over | 1 | 2 | 3 |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 60.9 | 62.7 | - |
| standard deviation | ± 10 | ± 10 | - |
| Gender Categorical | | | |
| Units: Subjects | | | |
| Female | 126 | 134 | 260 |
| Male | 191 | 186 | 377 |

End points

End points reporting groups

| | |
|------------------------------|---|
| Reporting group title | Vorinostat + Bortezomib |
| Reporting group description: | Participants will receive vorinostat four 100 mg capsules (400 mg total) orally 0-30 minutes after a meal on Days 1 through 14 of a 21-day treatment cycle and bortezomib 1.3 mg/m ² by intravenous injection on Days 1, 4, 8, and 11 of a 21-day treatment cycle. |
| Reporting group title | Placebo + Bortezomib |
| Reporting group description: | Participants will receive four placebo capsules orally 0-30 minutes after a meal on Days 1 through 14 of a 21-day treatment cycle and bortezomib 1.3 mg/m ² by intravenous injection on Days 1, 4, 8, and 11 Of a 21-day treatment cycle. |

Primary: Progression-Free Survival (PFS)

| | |
|------------------------|--|
| End point title | Progression-Free Survival (PFS) |
| End point description: | Progression-free survival was measured from the start of the treatment to the time when the criteria for progression was met or death due to any cause (whichever is first recorded). Response to study therapy was assessed using European Blood and Marrow Transplantation Group (EBMT) Criteria. A stratified Cox proportional hazards model was used with Efron's likelihood approximation to account for ties in event times. |
| End point type | Primary |
| End point timeframe: | From randomization to event of disease progression or death assessed up to 32 months (final study analysis) |

| End point values | Vorinostat + Bortezomib | Placebo + Bortezomib | | |
|----------------------------------|-------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 317 ^[1] | 320 ^[2] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 7.63 (6.87 to 8.4) | 6.83 (5.67 to 7.73) | | |

Notes:

[1] - Intention to treat (ITT) population including all randomized participants.

[2] - ITT population including all randomized participants.

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Ratio of Hazard Rates Assessed up to 32 Months |
| Comparison groups | Vorinostat + Bortezomib v Placebo + Bortezomib |
| Number of subjects included in analysis | 637 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.01 |
| Method | Regression, Cox |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 0.774 |

| | |
|---------------------|---------|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.636 |
| upper limit | 0.941 |

Secondary: Number of Participants with Clinical and Laboratory Adverse Events (AEs)

| | |
|-----------------|--|
| End point title | Number of Participants with Clinical and Laboratory Adverse Events (AEs) |
|-----------------|--|

End point description:

An adverse event (AE) was defined as any untoward medical occurrence in a participant administered a pharmaceutical product and which did not necessarily have to have a causal relationship with this treatment. An AE could therefore be any unfavorable and unintended sign, symptom, or disease temporally associated with the use of a medicinal product/protocol-specified procedure, whether or not considered related to the medicinal product/protocol-specified procedure. Any worsening of a preexisting condition temporally associated with the use of the product was also an AE.

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

End point timeframe:

From first dose up to 30 days after the last dose of study drug

| End point values | Vorinostat + Bortezomib | Placebo + Bortezomib | | |
|-----------------------------|-------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 315 ^[3] | 320 ^[4] | | |
| Units: Participants | 312 | 315 | | |

Notes:

[3] - All Patients as Treated population: all randomized participants who received ≥ 1 dose of study drug

[4] - All Patients as Treated population: all randomized participants who received ≥ 1 dose of study drug

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival

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

End point description:

Overall survival was measured from the start of the treatment to death due to any cause. Overall Survival is represented as the number of deaths per 100-person-months and was computed by dividing the number of participants with an event of death that occurred during the study follow-up period by the total duration of follow-up (in 100 months) for all the participants in each cohort since participants had different lengths of follow-up.

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

End point timeframe:

From randomization up to 32 months (final study analysis)

| End point values | Vorinostat + Bortezomib | Placebo + Bortezomib | | |
|----------------------------------|-------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 317 ^[5] | 320 ^[6] | | |
| Units: Events/100-person Months | | | | |
| number (confidence interval 95%) | 1.7 (1.56 to 1.84) | 1.9 (1.75 to 2.05) | | |

Notes:

[5] - ITT population including all randomized participants.

[6] - ITT population including all randomized participants.

Statistical analyses

| Statistical analysis title | Ratio of Hazard Rates Assessed up to 32 Months |
|---|--|
| Comparison groups | Vorinostat + Bortezomib v Placebo + Bortezomib |
| Number of subjects included in analysis | 637 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| Parameter estimate | Cox proportional hazard |
| Point estimate | 0.858 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.622 |
| upper limit | 1.184 |

Secondary: Time to Progression

| | |
|------------------------|--|
| End point title | Time to Progression |
| End point description: | Time to progression was measured from the start of the treatment to the time when the criteria for progression was met or death due to myeloma (whichever is first recorded). Response to study therapy was assessed using European Blood and Marrow Transplantation Group (EBMT) Criteria. A stratified Cox proportional hazards model was used with Efron's likelihood approximation to account for ties in event times. |
| End point type | Secondary |
| End point timeframe: | Baseline and at the end of each 21-day Cycle assessed up to 32 months (final study analysis) |

| End point values | Vorinostat + Bortezomib | Placebo + Bortezomib | | |
|----------------------------------|-------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 317 ^[7] | 320 ^[8] | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 7.73 (7 to 8.53) | 7.03 (6.33 to 7.73) | | |

Notes:

[7] - ITT population including all randomized participants.

[8] - ITT population including all randomized participants.

Statistical analyses

No statistical analyses for this end point

Secondary: Objective Response Rate

End point title | Objective Response Rate

End point description:

Objective response rate was measured as the proportion of patients who achieved a confirmed partial response or better during the course of the study. Response to study therapy was assessed using EBMT Criteria and confirmed by Independent Adjudication Review.

End point type | Secondary

End point timeframe:

Baseline and at the end of each 21-day Cycle assessed up to 32 months (final study analysis)

| End point values | Vorinostat + Bortezomib | Placebo + Bortezomib | | |
|-----------------------------------|-------------------------|----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 315 ^[9] | 320 ^[10] | | |
| Units: Percentage of Participants | | | | |
| number (confidence interval 95%) | 56.2 (50.5 to 61.7) | 40.6 (35.2 to 46.2) | | |

Notes:

[9] - Full Analysis Set: all randomized patient who received ≥ 1 dose of study treatment

[10] - Full Analysis Set: all randomized patient who received ≥ 1 dose of study treatment

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose up to 30 days after the last dose of study drug

Adverse event reporting additional description:

AEs were reported for the All Patients as Treated Population that included all randomized participants who received at least one dose of study treatment.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 14.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------------------|
| Reporting group title | Placebo + Bortezomib |
|-----------------------|----------------------|

Reporting group description:

Participants will receive four placebo capsules orally 0-30 minutes after a meal on Days 1 through 14 of a 21-day treatment cycle and bortezomib 1.3 mg/m² by intravenous injection on Days 1, 4, 8, and 11 of a 21-day treatment cycle.

| | |
|-----------------------|-------------------------|
| Reporting group title | Vorinostat + Bortezomib |
|-----------------------|-------------------------|

Reporting group description:

Participants will receive vorinostat four 100 mg capsules (400 mg total) orally 0-30 minutes after a meal on Days 1 through 14 of a 21-day treatment cycle and bortezomib 1.3 mg/m² by intravenous injection on Days 1, 4, 8, and 11 of a 21-day treatment cycle.

| Serious adverse events | Placebo + Bortezomib | Vorinostat + Bortezomib | |
|---|----------------------|-------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 138 / 320 (43.13%) | 130 / 315 (41.27%) | |
| number of deaths (all causes) | 17 | 11 | |
| number of deaths resulting from adverse events | 2 | 3 | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| B-cell lymphoma | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 2 / 320 (0.63%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colon cancer | | | |

| | | | |
|---|------------------|------------------|--|
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Neoplasm malignant | | | |
| subjects affected / exposed | 13 / 320 (4.06%) | 10 / 315 (3.17%) | |
| occurrences causally related to treatment / all | 0 / 13 | 0 / 10 | |
| deaths causally related to treatment / all | 0 / 5 | 0 / 4 | |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Circulatory collapse | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |
| subjects affected / exposed | 3 / 320 (0.94%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |
| subjects affected / exposed | 2 / 320 (0.63%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Orthostatic hypotension | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 320 (0.00%) | 4 / 315 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Shock | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (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 / 320 (0.31%) | 2 / 315 (0.63%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 2 / 320 (0.63%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 1 / 2 | 1 / 1 | |
| Fatigue | | | |
| subjects affected / exposed | 5 / 320 (1.56%) | 3 / 315 (0.95%) | |
| occurrences causally related to treatment / all | 6 / 6 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Generalised oedema | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multi-organ failure | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Pelvic mass | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (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 | 9 / 320 (2.81%) | 6 / 315 (1.90%) | |
| occurrences causally related to treatment / all | 4 / 12 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Swelling | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (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 respiratory failure | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Apnoea | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis chronic | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Dyspnoea exertional | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemoptysis | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 2 / 320 (0.63%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia aspiration | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 2 / 315 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumothorax | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |

| | | | |
|---|------------------|-------------------|--|
| subjects affected / exposed | 2 / 320 (0.63%) | 2 / 315 (0.63%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary hypertension | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Psychiatric disorders | | | |
| Anxiety disorder | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Completed suicide | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Accidental overdose | | | |
| subjects affected / exposed | 27 / 320 (8.44%) | 32 / 315 (10.16%) | |
| occurrences causally related to treatment / all | 0 / 43 | 0 / 52 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rib fracture | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Road traffic accident | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) | |
| 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 / 320 (0.00%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tibia fracture | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (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 / 320 (0.00%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arrhythmia | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 320 (0.63%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac failure | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 320 (0.00%) | 2 / 315 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiopulmonary failure | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 2 / 320 (0.63%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Ataxia | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Brain oedema | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) | |
| 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 | 1 / 320 (0.31%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral ischaemia | | | |

| | | |
|---|-----------------|-----------------|
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (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 | 1 / 320 (0.31%) | 0 / 315 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Cognitive disorder | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Diabetic coma | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (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 | 0 / 320 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Haemorrhage intracranial | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Headache | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Lethargy | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (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 | 2 / 320 (0.63%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paraplegia | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (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 | 4 / 320 (1.25%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 2 / 315 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 320 (0.63%) | 4 / 315 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 2 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone marrow failure | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 4 / 315 (1.27%) | |
| occurrences causally related to treatment / all | 0 / 0 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemolysis | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |

| | | | |
|---|------------------|-----------------|--|
| subjects affected / exposed | 1 / 320 (0.31%) | 2 / 315 (0.63%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 3 / 320 (0.94%) | 9 / 315 (2.86%) | |
| occurrences causally related to treatment / all | 1 / 3 | 11 / 13 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Deafness | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Constipation | | | |
| subjects affected / exposed | 2 / 320 (0.63%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 10 / 320 (3.13%) | 9 / 315 (2.86%) | |
| occurrences causally related to treatment / all | 9 / 10 | 12 / 12 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Gastritis | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhoids | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 2 / 315 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (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 | 2 / 320 (0.63%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Melaena | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (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 / 320 (0.94%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 4 / 4 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Odynophagia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophagitis | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 2 / 320 (0.63%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumatosis intestinalis | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 7 / 320 (2.19%) | 8 / 315 (2.54%) | |
| occurrences causally related to treatment / all | 6 / 8 | 7 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Hepatic necrosis | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Angioedema | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Decubitus ulcer | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rash maculo-papular | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (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 | | | |
| Azotaemia | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) | |
| 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 | 4 / 320 (1.25%) | 2 / 315 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Renal failure acute | | | |
| subjects affected / exposed | 2 / 320 (0.63%) | 2 / 315 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal impairment | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Hyperparathyroidism primary | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (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 | | | |
| Arthritis | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Bone pain | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spondylitis | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Synovial cyst | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 3 / 320 (0.94%) | 2 / 315 (0.63%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis pneumococcal | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchopneumonia | | | |

| | | |
|---|-----------------|-----------------|
| subjects affected / exposed | 1 / 320 (0.31%) | 4 / 315 (1.27%) |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 4 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 |
| Cellulitis | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Clostridial infection | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Clostridium difficile colitis | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 2 / 315 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Conjunctivitis bacterial | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Device related sepsis | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Escherichia sepsis | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Fungal infection | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Gastroenteritis | | |

| | | |
|---|-----------------|-----------------|
| subjects affected / exposed | 0 / 320 (0.00%) | 6 / 315 (1.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 7 / 9 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Gastroenteritis salmonella | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Gastroenteritis viral | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Gastrointestinal infection | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 2 / 315 (0.63%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Gastrointestinal viral infection | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| H1N1 influenza | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Haemophilus infection | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Hepatitis B | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Herpes simplex | | |

| | | |
|---|-----------------|-----------------|
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Herpes zoster | | |
| subjects affected / exposed | 6 / 320 (1.88%) | 0 / 315 (0.00%) |
| occurrences causally related to treatment / all | 3 / 6 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Herpes zoster ophthalmic | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Lobar pneumonia | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) |
| 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 | 2 / 320 (0.63%) | 2 / 315 (0.63%) |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 2 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 |
| Pharyngitis | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Pneumococcal sepsis | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Pneumonia | | |

| | | |
|---|------------------|------------------|
| subjects affected / exposed | 13 / 320 (4.06%) | 14 / 315 (4.44%) |
| occurrences causally related to treatment / all | 4 / 13 | 5 / 17 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Respiratory tract infection viral | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Sepsis | | |
| subjects affected / exposed | 5 / 320 (1.56%) | 0 / 315 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 |
| Septic shock | | |
| subjects affected / exposed | 3 / 320 (0.94%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 3 / 4 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Skin infection | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 1 / 315 (0.32%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Tracheobronchitis | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Tuberculosis | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 3 / 320 (0.94%) | 2 / 315 (0.63%) | |
| occurrences causally related to treatment / all | 1 / 3 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper respiratory tract infection bacterial | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 4 / 320 (1.25%) | 2 / 315 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Viral infection | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dehydration | | | |
| subjects affected / exposed | 5 / 320 (1.56%) | 2 / 315 (0.63%) | |
| occurrences causally related to treatment / all | 4 / 5 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 2 / 320 (0.63%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 2 / 315 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperuricaemia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (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 | 0 / 320 (0.00%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 1 / 315 (0.32%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 320 (0.00%) | 2 / 315 (0.63%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolic disorder | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour lysis syndrome | | | |
| subjects affected / exposed | 1 / 320 (0.31%) | 0 / 315 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

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

| Non-serious adverse events | Placebo + Bortezomib | Vorinostat + Bortezomib | |
|---|----------------------|-------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 306 / 320 (95.63%) | 312 / 315 (99.05%) | |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 11 / 320 (3.44%) | 17 / 315 (5.40%) | |
| occurrences (all) | 14 | 26 | |
| Weight decreased | | | |

| | | | |
|--|------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 22 / 320 (6.88%) 30 | 22 / 315 (6.98%) 36 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 13 / 320 (4.06%) | 29 / 315 (9.21%) | |
| occurrences (all) | 16 | 37 | |
| Hypotension | | | |
| subjects affected / exposed | 12 / 320 (3.75%) | 19 / 315 (6.03%) | |
| occurrences (all) | 15 | 23 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 27 / 320 (8.44%) | 36 / 315 (11.43%) | |
| occurrences (all) | 37 | 56 | |
| Dysgeusia | | | |
| subjects affected / exposed | 6 / 320 (1.88%) | 23 / 315 (7.30%) | |
| occurrences (all) | 8 | 28 | |
| Headache | | | |
| subjects affected / exposed | 34 / 320 (10.63%) | 35 / 315 (11.11%) | |
| occurrences (all) | 45 | 45 | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 18 / 320 (5.63%) | 10 / 315 (3.17%) | |
| occurrences (all) | 26 | 12 | |
| Neuralgia | | | |
| subjects affected / exposed | 86 / 320 (26.88%) | 82 / 315 (26.03%) | |
| occurrences (all) | 125 | 124 | |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 64 / 320 (20.00%) | 62 / 315 (19.68%) | |
| occurrences (all) | 97 | 94 | |
| Paraesthesia | | | |
| subjects affected / exposed | 12 / 320 (3.75%) | 20 / 315 (6.35%) | |
| occurrences (all) | 14 | 27 | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 27 / 320 (8.44%) | 33 / 315 (10.48%) | |
| occurrences (all) | 39 | 58 | |
| Blood and lymphatic system disorders | | | |

| | | | |
|--|--------------------|--------------------|--|
| Anaemia | | | |
| subjects affected / exposed | 79 / 320 (24.69%) | 91 / 315 (28.89%) | |
| occurrences (all) | 164 | 198 | |
| Leukopenia | | | |
| subjects affected / exposed | 32 / 320 (10.00%) | 42 / 315 (13.33%) | |
| occurrences (all) | 122 | 121 | |
| Neutropenia | | | |
| subjects affected / exposed | 95 / 320 (29.69%) | 112 / 315 (35.56%) | |
| occurrences (all) | 300 | 406 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 106 / 320 (33.13%) | 172 / 315 (54.60%) | |
| occurrences (all) | 384 | 749 | |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 40 / 320 (12.50%) | 46 / 315 (14.60%) | |
| occurrences (all) | 80 | 89 | |
| Fatigue | | | |
| subjects affected / exposed | 96 / 320 (30.00%) | 125 / 315 (39.68%) | |
| occurrences (all) | 176 | 350 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 24 / 320 (7.50%) | 24 / 315 (7.62%) | |
| occurrences (all) | 27 | 28 | |
| Pyrexia | | | |
| subjects affected / exposed | 70 / 320 (21.88%) | 66 / 315 (20.95%) | |
| occurrences (all) | 130 | 114 | |
| Gastrointestinal disorders | | | |
| Abdominal distension | | | |
| subjects affected / exposed | 17 / 320 (5.31%) | 8 / 315 (2.54%) | |
| occurrences (all) | 21 | 11 | |
| Abdominal pain | | | |
| subjects affected / exposed | 27 / 320 (8.44%) | 22 / 315 (6.98%) | |
| occurrences (all) | 40 | 37 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 13 / 320 (4.06%) | 26 / 315 (8.25%) | |
| occurrences (all) | 20 | 42 | |
| Constipation | | | |

| | | | |
|--|---------------------------|---------------------------|--|
| subjects affected / exposed occurrences (all) | 86 / 320 (26.88%) 132 | 64 / 315 (20.32%) 91 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 133 / 320 (41.56%) 275 | 194 / 315 (61.59%) 604 | |
| Dyspepsia subjects affected / exposed occurrences (all) | 26 / 320 (8.13%) 40 | 24 / 315 (7.62%) 38 | |
| Nausea subjects affected / exposed occurrences (all) | 126 / 320 (39.38%) 247 | 193 / 315 (61.27%) 457 | |
| Vomiting subjects affected / exposed occurrences (all) | 80 / 320 (25.00%) 127 | 140 / 315 (44.44%) 280 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 48 / 320 (15.00%) 61 | 52 / 315 (16.51%) 71 | |
| Dyspnoea subjects affected / exposed occurrences (all) | 28 / 320 (8.75%) 35 | 26 / 315 (8.25%) 36 | |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 13 / 320 (4.06%) 16 | 16 / 315 (5.08%) 17 | |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia subjects affected / exposed occurrences (all) | 3 / 320 (0.94%) 3 | 24 / 315 (7.62%) 26 | |
| Rash subjects affected / exposed occurrences (all) | 40 / 320 (12.50%) 61 | 31 / 315 (9.84%) 43 | |
| Psychiatric disorders | | | |
| Insomnia subjects affected / exposed occurrences (all) | 29 / 320 (9.06%) 36 | 28 / 315 (8.89%) 32 | |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|------------------------------------|-------------------|-------------------|--|
| Arthralgia | | | |
| subjects affected / exposed | 27 / 320 (8.44%) | 26 / 315 (8.25%) | |
| occurrences (all) | 40 | 34 | |
| Back pain | | | |
| subjects affected / exposed | 47 / 320 (14.69%) | 49 / 315 (15.56%) | |
| occurrences (all) | 69 | 67 | |
| Bone pain | | | |
| subjects affected / exposed | 24 / 320 (7.50%) | 15 / 315 (4.76%) | |
| occurrences (all) | 39 | 27 | |
| Muscle spasms | | | |
| subjects affected / exposed | 15 / 320 (4.69%) | 21 / 315 (6.67%) | |
| occurrences (all) | 17 | 25 | |
| Pain in extremity | | | |
| subjects affected / exposed | 38 / 320 (11.88%) | 16 / 315 (5.08%) | |
| occurrences (all) | 52 | 21 | |
| Infections and infestations | | | |
| Herpes zoster | | | |
| subjects affected / exposed | 19 / 320 (5.94%) | 22 / 315 (6.98%) | |
| occurrences (all) | 21 | 26 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 18 / 320 (5.63%) | 16 / 315 (5.08%) | |
| occurrences (all) | 20 | 22 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 38 / 320 (11.88%) | 55 / 315 (17.46%) | |
| occurrences (all) | 58 | 76 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 85 / 320 (26.56%) | 75 / 315 (23.81%) | |
| occurrences (all) | 139 | 123 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 25 / 320 (7.81%) | 35 / 315 (11.11%) | |
| occurrences (all) | 40 | 57 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 24 June 2009 | Global substantial Amendment 1 revised the study flow chart and reduced the eligibility criteria for minimal acceptable renal function at study entry. |
| 06 January 2010 | Global substantial Amendment 2 added a dose modification summary table and updated dose modification guidelines to clarify the sequence of drug modifications and whether modification was required or optional for each agent. Supportive care recommendations were also added. |
| 05 November 2010 | Global substantial Amendment 3 revised the study design to delete the second interim analysis, increase the efficacy target at final analysis, and to move the final analysis to an earlier date. |
| 17 March 2011 | Global substantial Amendment 4 incorporated end of study procedures and added an extension phase for the study. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported