



Clinical trial results:

A Randomized, Open-label, Phase 3 Study of Carfilzomib vs Best Supportive Care in Subjects with Relapsed and Refractory Multiple Myeloma

Summary

| | |
|--------------------------|----------------------------------|
| EudraCT number | 2009-016840-38 |
| Trial protocol | AT HU CZ ES IT GB SE SK GR DE BE |
| Global end of trial date | 03 November 2015 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 19 September 2016 |
| First version publication date | 19 September 2016 |

Trial information

Trial identification

| | |
|-----------------------|------------|
| Sponsor protocol code | PX-171-011 |
|-----------------------|------------|

Additional study identifiers

| | |
|------------------------------------|--------------------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01302392 |
| WHO universal trial number (UTN) | - |
| Other trial identifiers | Amgen Study ID: 20130396 |

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|------------------|
| Analysis stage | Final |
| Date of interim/final analysis | 10 July 2014 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 03 November 2015 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

This is a Phase 3, randomized, open-label, multicenter study comparing two treatment regimens for subjects with multiple myeloma who have received all available approved treatment options and may therefore be considered candidates for palliative care.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines. Essential documents will be retained in accordance with ICH GCP.

All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures.

The study protocol, amendments, and the informed consent form (ICF) were reviewed by the Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). No subjects were recruited into the study and no investigational product (IP) was shipped until the IRB/IEC gave written approval of the protocol and ICF and Amgen received copies of these approvals.

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 06 September 2010 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Australia: 3 |
| Country: Number of subjects enrolled | Austria: 17 |
| Country: Number of subjects enrolled | Belgium: 11 |
| Country: Number of subjects enrolled | Czech Republic: 35 |
| Country: Number of subjects enrolled | France: 9 |
| Country: Number of subjects enrolled | Germany: 11 |
| Country: Number of subjects enrolled | Greece: 13 |
| Country: Number of subjects enrolled | Hungary: 42 |
| Country: Number of subjects enrolled | Israel: 28 |
| Country: Number of subjects enrolled | Italy: 45 |
| Country: Number of subjects enrolled | New Zealand: 1 |
| Country: Number of subjects enrolled | Poland: 16 |
| Country: Number of subjects enrolled | Russian Federation: 9 |
| Country: Number of subjects enrolled | Serbia: 3 |
| Country: Number of subjects enrolled | Slovakia: 2 |

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Korea, Republic of: 5 |
| Country: Number of subjects enrolled | Spain: 42 |
| Country: Number of subjects enrolled | Sweden: 1 |
| Country: Number of subjects enrolled | United Kingdom: 22 |
| Worldwide total number of subjects | 315 |
| EEA total number of subjects | 266 |

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) | 151 |
| From 65 to 84 years | 163 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

Subjects were enrolled from 06 September 2010 to 21 October 2012. Results are reported as of the data cut-off date of 10 Jul 2014.

Pre-assignment

Screening details:

Eligible subjects were randomized in a 1:1 ratio to carfilzomib or best supportive care. Randomization was stratified based on the number of previous therapies (3 versus 4 versus ≥ 5) and geographical region (Europe versus non-Europe).

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 | Best Supportive Care |

Arm description:

Subjects received corticosteroids (either prednisolone 30 mg orally (PO) every other day, dexamethasone 6 mg PO every other day, or other equivalent corticosteroid) for a maximum of 84 mg dexamethasone, or equivalent, per 28-day cycle. Additionally, optional cyclophosphamide (50 mg/day; maximum 1400 mg per 28-day cycle) could be given.

| | |
|--|-----------------------------|
| Arm type | Active comparator |
| Investigational medicinal product name | Corticosteroid |
| Investigational medicinal product code | |
| Other name | prednisolone, dexamethasone |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Either prednisolone 30 mg every other day, dexamethasone 6 mg every other day, or equivalent corticosteroid regimen

| | |
|------------------|-------------|
| Arm title | Carfilzomib |
|------------------|-------------|

Arm description:

Subjects received carfilzomib 20 mg/m² IV on Days 1 and 2 of Cycle 1, escalating to 27 mg/m² IV on Days 8, 9, 15, and 16 of Cycle 1 and continuing on Days 1, 2, 8, 9, 15, and 16 of Cycles 2 through Cycle 9. Cycles 10 and beyond received 27 mg/m² IV on Days 1, 2, 15, and 16 (alternatively, the investigator could choose to continue the dosing frequency on the original dosing days [Days 1, 2, 8, 9, 15, 16] for individual subjects).

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

Dosage and administration details:

Administered by intravenous infusion 20 mg/m² IV on Days 1 and 2 of Cycle 1, escalating to 27 mg/m² IV on Days 8, 9, 15, and 16 of Cycle 1 and continuing on Days 1, 2, 8, 9, 15, and 16 of Cycle 2 through Cycle 9. From cycle 10, 27 mg/m² (or at the last dose given in Cycle 9) IV on Days 1, 2, 15, and 16 (omitting Days 8 and 9) unless the Investigator chose to reinstate the dosing frequency to the original regimen (Days 1, 2, 8, 9, 15,16) for individual patients.

| Number of subjects in period 1 | Best Supportive Care | Carfilzomib |
|---------------------------------------|----------------------|-------------|
| Started | 158 | 157 |
| Treated | 153 | 157 |
| Completed | 151 | 156 |
| Not completed | 7 | 1 |
| Consent withdrawn by subject | 6 | 1 |
| Lost to follow-up | 1 | - |

Baseline characteristics

Reporting groups

| | |
|--|----------------------|
| Reporting group title | Best Supportive Care |
| Reporting group description: | |
| Subjects received corticosteroids (either prednisolone 30 mg orally (PO) every other day, dexamethasone 6 mg PO every other day, or other equivalent corticosteroid) for a maximum of 84 mg dexamethasone, or equivalent, per 28-day cycle. Additionally, optional cyclophosphamide (50 mg/day; maximum 1400 mg per 28-day cycle) could be given. | |
| Reporting group title | Carfilzomib |
| Reporting group description: | |
| Subjects received carfilzomib 20 mg/m ² IV on Days 1 and 2 of Cycle 1, escalating to 27 mg/m ² IV on Days 8, 9, 15, and 16 of Cycle 1 and continuing on Days 1, 2, 8, 9, 15, and 16 of Cycles 2 through Cycle 9. Cycles 10 and beyond received 27 mg/m ² IV on Days 1, 2, 15, and 16 (alternatively, the investigator could choose to continue the dosing frequency on the original dosing days [Days 1, 2, 8, 9, 15, 16] for individual subjects). | |

| Reporting group values | Best Supportive Care | Carfilzomib | Total |
|--|----------------------|-------------|-------|
| Number of subjects | 158 | 157 | 315 |
| Age categorical | | | |
| Units: Subjects | | | |
| < 65 years | 83 | 68 | 151 |
| ≥ 65 years | 75 | 89 | 164 |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 65.5 | 63.3 | |
| standard deviation | ± 8.02 | ± 10.71 | - |
| Gender, Male/Female | | | |
| Units: participants | | | |
| Female | 62 | 75 | 137 |
| Male | 96 | 82 | 178 |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 4 | 1 | 5 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 1 | 1 | 2 |
| White | 148 | 151 | 299 |
| Other | 5 | 4 | 9 |
| Region | | | |
| Units: Subjects | | | |
| Europe | 138 | 140 | 278 |
| Non-Europe | 20 | 17 | 37 |
| Number of Prior Regimens to Treat Multiple Myeloma | | | |
| Units: Subjects | | | |
| 3 regimens | 19 | 17 | 36 |
| 4 regimens | 35 | 34 | 69 |
| ≥ 5 regimens | 104 | 106 | 210 |

End points

End points reporting groups

| | |
|--|----------------------|
| Reporting group title | Best Supportive Care |
| Reporting group description: Subjects received corticosteroids (either prednisolone 30 mg orally (PO) every other day, dexamethasone 6 mg PO every other day, or other equivalent corticosteroid) for a maximum of 84 mg dexamethasone, or equivalent, per 28-day cycle. Additionally, optional cyclophosphamide (50 mg/day; maximum 1400 mg per 28-day cycle) could be given. | |
| Reporting group title | Carfilzomib |
| Reporting group description: Subjects received carfilzomib 20 mg/m ² IV on Days 1 and 2 of Cycle 1, escalating to 27 mg/m ² IV on Days 8, 9, 15, and 16 of Cycle 1 and continuing on Days 1, 2, 8, 9, 15, and 16 of Cycles 2 through Cycle 9. Cycles 10 and beyond received 27 mg/m ² IV on Days 1, 2, 15, and 16 (alternatively, the investigator could choose to continue the dosing frequency on the original dosing days [Days 1, 2, 8, 9, 15, 16] for individual subjects). | |

Primary: Overall Survival

| | |
|--|------------------|
| End point title | Overall Survival |
| End point description: Time elapsed between the randomization date and the date of death. Participants who were still alive were censored at the date when the subject was last known alive or the data cutoff date, whichever occurred earlier. | |
| End point type | Primary |
| End point timeframe: From randomization through the final analysis data cutoff with longest follow-up time of approximately 45 months. Median follow up times were 27.8 months and 29.8 months for Carfilzomib and Best Supportive Care groups, respectively. | |

| End point values | Best Supportive Care | Carfilzomib | | |
|----------------------------------|----------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 158 | 157 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 10 (7.7 to 12) | 10.2 (8.4 to 14.4) | | |

Statistical analyses

| | |
|----------------------------|------------------------------------|
| Statistical analysis title | Analysis of Overall Survival |
| Comparison groups | Best Supportive Care v Carfilzomib |

| | |
|---|-------------------------|
| Number of subjects included in analysis | 315 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.4172 ^[1] |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.975 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.76 |
| upper limit | 1.249 |

Notes:

[1] - P value was from stratified log-rank test with number of previous therapies (3 versus 4 versus ≥ 5) and geographical region (Europe versus non-Europe) as stratification factors.

Secondary: Progression-free Survival

| | |
|-----------------|---------------------------|
| End point title | Progression-free Survival |
|-----------------|---------------------------|

End point description:

Kaplan-Meier estimate of median time from randomization to progressive disease (PD) or all-cause death. PD was assessed using International Myeloma Working Group-Uniform Response Criteria (IMWG-URC). 1 or more conditions were required to meet PD: 2 consecutive rising serum or urine M-protein from central lab; documented new bone lesion(s) or soft tissue plasmacytoma(s) or increased size of existing bone lesion(s) or plasmacytoma(s); or confirmed hypercalcemia due solely to plasma cell proliferative disorder (local lab greater than 11.5 mg/dL on 2 separate occasions). Censoring conditions (censoring dates) were: no post-baseline disease assessment (DA) (randomization date); started non-protocol systemic anticancer treatment before PD or death (last DA date before such treatment); died or had PD after more than 1 missed DA (last DA date without PD before the first missed visit); or were alive and without documentation of PD, including lost to follow-up without PD (last DA date).

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

End point timeframe:

From randomization through the final analysis data cutoff with longest follow-up time of approximately 31 months. Median follow up times were 26.6 months and 23.1 months for Carfilzomib and Best Supportive Care groups, respectively.

| End point values | Best Supportive Care | Carfilzomib | | |
|----------------------------------|----------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 158 | 157 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 3.3 (2.2 to 5.2) | 3.7 (2.8 to 4.2) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Response

| | |
|-----------------|------------------|
| End point title | Overall Response |
|-----------------|------------------|

End point description:

Number of participants who achieved confirmed stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR) as their best response. Response was determined using the International Myeloma Working Group - Uniform Response Criteria (IMWG-URC).

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

End point timeframe:

From randomization through the final analysis data cutoff with longest follow-up time of approximately 31 months. Median follow up times were 26.6 months and 23.1 months for Carfilzomib and Best Supportive Care groups, respectively.

| End point values | Best Supportive Care | Carfilzomib | | |
|-----------------------------|----------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 158 | 157 | | |
| Units: participants | | | | |
| number (not applicable) | 18 | 30 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

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

End point description:

Duration of response (DOR) was calculated for subjects who achieved a best response of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR). Duration of response was defined as the time in months from the initial start of response (PR or better) to the earlier of documented progressive disease (PD) or death due to any cause. Participants who had not progressed or died were censored according to the censoring rules defined previously for progression-free survival. "99999" indicates not calculable due to a low number of participants reaching PD or all-cause death.

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

End point timeframe:

From the time achieving response through the final analysis data cutoff with longest follow-up time of approximately 29 months.

| End point values | Best Supportive Care | Carfilzomib | | |
|----------------------------------|----------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 18 | 30 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 9.5 (3.7 to 99999) | 7.2 (4.6 to 12) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Clinical Benefit Response

| | |
|-----------------|---------------------------|
| End point title | Clinical Benefit Response |
|-----------------|---------------------------|

End point description:

Number of participants who achieved confirmed stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), or minimal response (MR) as their best response. Response was determined using the International Myeloma Working Group - Uniform Response Criteria (IMWG-URC). (MR was determined using European Group for Blood and Marrow Transplantation criteria)

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

End point timeframe:

From randomization through the final analysis data cutoff with longest follow-up time of approximately 31 months. Median follow up times were 26.6 months and 23.1 months for Carfilzomib and Best Supportive Care groups, respectively.

| End point values | Best Supportive Care | Carfilzomib | | |
|-----------------------------|----------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 158 | 157 | | |
| Units: participants | | | | |
| number (not applicable) | 33 | 49 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Clinical Benefit

| | |
|-----------------|------------------------------|
| End point title | Duration of Clinical Benefit |
|-----------------|------------------------------|

End point description:

Duration of Clinical Benefit was calculated for subjects who achieved a best response of stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR) or minimal response (MR). Duration of Clinical Benefit was defined as the time in months from the initial start of response (MR or better) to the earlier of documented progressive disease (PD) or death due to any cause. Participants who had not progressed or died were censored according to the censoring rules defined previously for progression-free survival.

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

End point timeframe:

From time of achieving clinical benefit through the final analysis data cutoff with longest follow-up time of approximately 30 months.

| End point values | Best Supportive Care | Carfilzomib | | |
|----------------------------------|----------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 33 | 49 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 8.3 (6.5 to 12.9) | 6.4 (4.9 to 8.3) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Disease Control

| | |
|--|-----------------|
| End point title | Disease Control |
| End point description: | |
| Number of participants who achieved confirmed stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), minimal response (MR), or stable disease (SD) lasting ≥ 8 weeks as their best response. Response was determined using the International Myeloma Working Group - Uniform Response Criteria (IMWG-URC). (MR was determined using European Group for Blood and Marrow Transplantation criteria) | |
| End point type | Secondary |
| End point timeframe: | |
| From randomization through the final analysis data cutoff with longest follow-up time of approximately 31 months. Median follow up times were 26.6 months and 23.1 months for Carfilzomib and Best Supportive Care groups, respectively. | |

| End point values | Best Supportive Care | Carfilzomib | | |
|-----------------------------|----------------------|-----------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 158 | 157 | | |
| Units: participants | | | | |
| number (not applicable) | 107 | 119 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Disease Control

| | |
|--|-----------------------------|
| End point title | Duration of Disease Control |
| End point description: | |
| Duration of Disease Control was calculated for subjects who achieved disease control. Duration of Disease Control was defined as the time in months from randomization to the earlier of documented progressive disease (PD) or death due to any cause. Participants who had not progressed or died were censored according to the censoring rules defined previously for progression-free survival. | |
| End point type | Secondary |

End point timeframe:

From time of achieving disease control through the final analysis data cutoff with longest follow-up time of approximately 31 months.

| End point values | Best Supportive Care | Carfilzomib | | |
|----------------------------------|----------------------|------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 107 | 119 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 6.6 (5.4 to 8.8) | 5.5 (3.9 to 6.5) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From randomization through the final analysis data cutoff with range of follow-up time of 0.4 - 138.3 weeks with median of 10.7 weeks in Best Supportive Care arm, and 0.3 - 138.4 weeks with median of 16.3 weeks in carfilzomib arm.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 15.1 |

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Carfilzomib |
|-----------------------|-------------|

Reporting group description:

Participants received carfilzomib 20 mg/m² IV on Days 1 and 2 of Cycle 1, escalating to 27 mg/m² IV on Days 8, 9, 15, and 16 of Cycle 1 and continuing on Days 1, 2, 8, 9, 15, and 16 of Cycles 2 through Cycle 9. Cycles 10 and beyond received 27 mg/m² IV on Days 1, 2, 15, and 16 (alternatively, the investigator could choose to continue the dosing frequency on the original dosing days [Days 1, 2, 8, 9, 15, 16] for individual subjects).

| | |
|-----------------------|----------------------|
| Reporting group title | Best Supportive Care |
|-----------------------|----------------------|

Reporting group description:

Subjects received corticosteroids (either prednisolone 30 mg orally (PO) every other day, dexamethasone 6 mg PO every other day, or other equivalent corticosteroid) for a maximum of 84 mg dexamethasone, or equivalent, per 28-day cycle. Additionally, optional cyclophosphamide (50 mg/day; maximum 1400 mg per 28-day cycle) could be given.

| Serious adverse events | Carfilzomib | Best Supportive Care | |
|---|-------------------|----------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 92 / 157 (58.60%) | 78 / 153 (50.98%) | |
| number of deaths (all causes) | 129 | 123 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Acute myeloid leukaemia | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hepatic neoplasm malignant | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukaemia plasmacytic | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malignant pleural effusion | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 2 / 157 (1.27%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Venous thrombosis | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (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 | 0 / 157 (0.00%) | 2 / 153 (1.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest pain | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Death | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

| | | | |
|---|-------------------|-------------------|--|
| Disease progression | | | |
| subjects affected / exposed | 16 / 157 (10.19%) | 19 / 153 (12.42%) | |
| occurrences causally related to treatment / all | 0 / 16 | 0 / 19 | |
| deaths causally related to treatment / all | 0 / 14 | 0 / 14 | |
| General physical health deterioration | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Malaise | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 153 (0.65%) | |
| 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 | 2 / 157 (1.27%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 6 / 157 (3.82%) | 2 / 153 (1.31%) | |
| occurrences causally related to treatment / all | 3 / 8 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Immune system disorders | | | |
| Anaphylactic reaction | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Reproductive system and breast | | | |

| | | | |
|---|-----------------|-----------------|--|
| disorders | | | |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Dyspnoea | | | |
| subjects affected / exposed | 2 / 157 (1.27%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epistaxis | | | |
| subjects affected / exposed | 2 / 157 (1.27%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary congestion | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |

| | | | |
|---|-----------------|-----------------|--|
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pulmonary oedema | | | |
| subjects affected / exposed | 2 / 157 (1.27%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Psychiatric disorders | | | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Hepatic enzyme increased | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hip fracture | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar vertebral fracture | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Periprosthetic fracture | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thoracic vertebral fracture | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sternal fracture | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Acute left ventricular failure | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 2 / 157 (1.27%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 1 | |
| Cardiac failure | | | |
| subjects affected / exposed | 4 / 157 (2.55%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 1 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 1 | |
| Cardiac failure acute | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 2 / 157 (1.27%) | 3 / 153 (1.96%) | |
| occurrences causally related to treatment / all | 1 / 2 | 3 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Convulsion | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Coma | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dizziness | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemorrhage intracranial | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paraparesis | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (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 | 2 / 157 (1.27%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 4 / 157 (2.55%) | 8 / 153 (5.23%) | |
| occurrences causally related to treatment / all | 1 / 6 | 3 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 3 / 157 (1.91%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 3 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperviscosity syndrome | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukocytosis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leukopenia | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 3 / 153 (1.96%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 3 / 157 (1.91%) | 5 / 153 (3.27%) | |
| occurrences causally related to treatment / all | 1 / 5 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Ulcerative keratitis | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulum intestinal | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haematemesis | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (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 | 1 / 157 (0.64%) | 2 / 153 (1.31%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 2 / 153 (1.31%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Biliary colic | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |

| | | | |
|---|------------------|-----------------|--|
| Hydronephrosis | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oliguria | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure | | | |
| subjects affected / exposed | 3 / 157 (1.91%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal failure acute | | | |
| subjects affected / exposed | 15 / 157 (9.55%) | 6 / 153 (3.92%) | |
| occurrences causally related to treatment / all | 1 / 15 | 2 / 7 | |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | |
| Renal impairment | | | |
| subjects affected / exposed | 2 / 157 (1.27%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |
| subjects affected / exposed | 6 / 157 (3.82%) | 3 / 153 (1.96%) | |
| occurrences causally related to treatment / all | 0 / 6 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone pain | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 2 / 153 (1.31%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Joint effusion | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (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 | 2 / 157 (1.27%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteolysis | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteoporosis | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pathological fracture | | | |
| subjects affected / exposed | 2 / 157 (1.27%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |

| | | | |
|---|-----------------|-----------------|--|
| Bacteraemia | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 3 / 157 (1.91%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 3 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchopneumonia | | | |
| subjects affected / exposed | 6 / 157 (3.82%) | 5 / 153 (3.27%) | |
| occurrences causally related to treatment / all | 1 / 6 | 2 / 5 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lobar pneumonia | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Kidney infection | | | |

| | | | |
|---|------------------|-------------------|--|
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Meningitis | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metapneumovirus infection | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Periorbital cellulitis | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 10 / 157 (6.37%) | 18 / 153 (11.76%) | |
| occurrences causally related to treatment / all | 3 / 11 | 5 / 22 | |
| deaths causally related to treatment / all | 0 / 1 | 2 / 7 | |
| Pneumonia pneumococcal | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia streptococcal | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 3 / 157 (1.91%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 4 / 153 (2.61%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 7 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis syndrome | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 3 / 153 (1.96%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 2 | |
| Staphylococcal sepsis | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Tracheobronchitis | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (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 | 3 / 157 (1.91%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 7 / 157 (4.46%) | 4 / 153 (2.61%) | |
| occurrences causally related to treatment / all | 1 / 9 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperkalaemia | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 157 (0.64%) | 2 / 153 (1.31%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperuricaemia | | | |
| subjects affected / exposed | 0 / 157 (0.00%) | 1 / 153 (0.65%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Tumour lysis syndrome | | | |
| subjects affected / exposed | 3 / 157 (1.91%) | 0 / 153 (0.00%) | |
| occurrences causally related to treatment / all | 4 / 4 | 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 | Carfilzomib | Best Supportive Care | |
|---|--------------------|-----------------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 141 / 157 (89.81%) | 135 / 153 (88.24%) | |
| Investigations | | | |
| Creatinine renal clearance decreased | | | |
| subjects affected / exposed | 9 / 157 (5.73%) | 4 / 153 (2.61%) | |
| occurrences (all) | 23 | 6 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 13 / 157 (8.28%) | 10 / 153 (6.54%) | |
| occurrences (all) | 21 | 15 | |
| Neutrophil count decreased | | | |
| subjects affected / exposed | 13 / 157 (8.28%) | 10 / 153 (6.54%) | |
| occurrences (all) | 21 | 19 | |
| Platelet count decreased | | | |
| subjects affected / exposed | 12 / 157 (7.64%) | 12 / 153 (7.84%) | |
| occurrences (all) | 33 | 20 | |
| Vascular disorders | | | |
| Hypertension | | | |
| subjects affected / exposed | 23 / 157 (14.65%) | 9 / 153 (5.88%) | |
| occurrences (all) | 31 | 11 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 10 / 157 (6.37%) | 3 / 153 (1.96%) | |
| occurrences (all) | 21 | 4 | |
| Headache | | | |
| subjects affected / exposed | 17 / 157 (10.83%) | 6 / 153 (3.92%) | |
| occurrences (all) | 23 | 8 | |
| Blood and lymphatic system disorders | | | |
| Leukopenia | | | |
| subjects affected / exposed | 9 / 157 (5.73%) | 15 / 153 (9.80%) | |
| occurrences (all) | 37 | 48 | |
| Neutropenia | | | |
| subjects affected / exposed | 22 / 157 (14.01%) | 23 / 153 (15.03%) | |
| occurrences (all) | 73 | 45 | |
| Anaemia | | | |
| subjects affected / exposed | 88 / 157 (56.05%) | 72 / 153 (47.06%) | |
| occurrences (all) | 275 | 212 | |

| | | | |
|---|--------------------------|--------------------------|--|
| Thrombocytopenia subjects affected / exposed occurrences (all) | 58 / 157 (36.94%) 231 | 43 / 153 (28.10%) 102 | |
| General disorders and administration site conditions | | | |
| Asthenia subjects affected / exposed occurrences (all) | 26 / 157 (16.56%) 44 | 20 / 153 (13.07%) 27 | |
| Chest pain subjects affected / exposed occurrences (all) | 5 / 157 (3.18%) 6 | 8 / 153 (5.23%) 8 | |
| Chills subjects affected / exposed occurrences (all) | 8 / 157 (5.10%) 11 | 1 / 153 (0.65%) 1 | |
| Fatigue subjects affected / exposed occurrences (all) | 29 / 157 (18.47%) 55 | 28 / 153 (18.30%) 46 | |
| Oedema peripheral subjects affected / exposed occurrences (all) | 17 / 157 (10.83%) 22 | 12 / 153 (7.84%) 14 | |
| Pain subjects affected / exposed occurrences (all) | 8 / 157 (5.10%) 11 | 1 / 153 (0.65%) 2 | |
| Pyrexia subjects affected / exposed occurrences (all) | 41 / 157 (26.11%) 92 | 28 / 153 (18.30%) 34 | |
| Gastrointestinal disorders | | | |
| Constipation subjects affected / exposed occurrences (all) | 10 / 157 (6.37%) 14 | 20 / 153 (13.07%) 22 | |
| Diarrhoea subjects affected / exposed occurrences (all) | 23 / 157 (14.65%) 37 | 18 / 153 (11.76%) 19 | |
| Dyspepsia subjects affected / exposed occurrences (all) | 10 / 157 (6.37%) 12 | 4 / 153 (2.61%) 5 | |
| Vomiting | | | |

| | | | |
|---|-------------------------|-------------------------|--|
| subjects affected / exposed occurrences (all) | 15 / 157 (9.55%) 25 | 5 / 153 (3.27%) 6 | |
| Nausea subjects affected / exposed occurrences (all) | 31 / 157 (19.75%) 50 | 14 / 153 (9.15%) 15 | |
| Respiratory, thoracic and mediastinal disorders Epistaxis subjects affected / exposed occurrences (all) | 12 / 157 (7.64%) 17 | 10 / 153 (6.54%) 20 | |
| Dyspnoea subjects affected / exposed occurrences (all) | 21 / 157 (13.38%) 36 | 12 / 153 (7.84%) 12 | |
| Cough subjects affected / exposed occurrences (all) | 19 / 157 (12.10%) 27 | 10 / 153 (6.54%) 12 | |
| Psychiatric disorders Insomnia subjects affected / exposed occurrences (all) | 4 / 157 (2.55%) 4 | 18 / 153 (11.76%) 22 | |
| Renal and urinary disorders Renal failure subjects affected / exposed occurrences (all) | 8 / 157 (5.10%) 8 | 3 / 153 (1.96%) 5 | |
| Renal impairment subjects affected / exposed occurrences (all) | 11 / 157 (7.01%) 33 | 5 / 153 (3.27%) 9 | |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 11 / 157 (7.01%) 14 | 6 / 153 (3.92%) 8 | |
| Back pain subjects affected / exposed occurrences (all) | 13 / 157 (8.28%) 15 | 16 / 153 (10.46%) 23 | |
| Bone pain subjects affected / exposed occurrences (all) | 18 / 157 (11.46%) 25 | 16 / 153 (10.46%) 20 | |

| | | | |
|---|-------------------------|------------------------|--|
| Pain in extremity subjects affected / exposed occurrences (all) | 13 / 157 (8.28%) 16 | 7 / 153 (4.58%) 7 | |
| Musculoskeletal pain subjects affected / exposed occurrences (all) | 5 / 157 (3.18%) 6 | 10 / 153 (6.54%) 12 | |
| Infections and infestations | | | |
| Bronchitis subjects affected / exposed occurrences (all) | 13 / 157 (8.28%) 22 | 13 / 153 (8.50%) 14 | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 13 / 157 (8.28%) 23 | 10 / 153 (6.54%) 14 | |
| Respiratory tract infection subjects affected / exposed occurrences (all) | 10 / 157 (6.37%) 14 | 6 / 153 (3.92%) 7 | |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 16 / 157 (10.19%) 26 | 3 / 153 (1.96%) 3 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 9 / 157 (5.73%) 10 | 7 / 153 (4.58%) 9 | |
| Hypercalcaemia subjects affected / exposed occurrences (all) | 13 / 157 (8.28%) 25 | 9 / 153 (5.88%) 14 | |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 6 / 157 (3.82%) 10 | 8 / 153 (5.23%) 14 | |
| Hyperkalaemia subjects affected / exposed occurrences (all) | 8 / 157 (5.10%) 14 | 2 / 153 (1.31%) 2 | |
| Hyperuricaemia subjects affected / exposed occurrences (all) | 19 / 157 (12.10%) 20 | 10 / 153 (6.54%) 16 | |
| Hypocalcaemia | | | |

| | | | |
|-----------------------------|------------------|------------------|--|
| subjects affected / exposed | 11 / 157 (7.01%) | 10 / 153 (6.54%) | |
| occurrences (all) | 20 | 15 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 14 / 157 (8.92%) | 13 / 153 (8.50%) | |
| occurrences (all) | 25 | 16 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 11 / 157 (7.01%) | 11 / 153 (7.19%) | |
| occurrences (all) | 23 | 14 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 31 March 2011 | 1) In order to adhere to CHMP guidance to design a study with survival as the primary endpoint, the primary endpoint was changed from PFS to OS. This was accompanied by an increase in sample size from 84 to 302 in order to provide 80% power to detect a 43% increase in OS for carfilzomib over control. A regional stratification variable was added to control for the additional sites and countries that were added for the increased sample size. 2) The window provided in Inclusion Criterion 2 to demonstrate measurable disease by central laboratory analysis of M-proteins was increased from 14 days originally to 21 days in order to account for the challenges in logistics of trans-country sample shipment followed by analysis and review. |
| 08 March 2012 | 1) The interim analysis at 50% of the total number of OS events was removed, and the interim analysis of OS at approximately 75% of the total number of OS events was retained to ensure that the data were mature at the time of the interim analysis and to adhere to CHMP guidance. 2) Inclusion Criterion 11, which required prior treatment with anthracycline, was eliminated in order to expand study access to subjects being managed per current standard of care which does not support the routine use of anthracyclines. 3) Exclusion Criterion 21, which excluded subjects with any contraindications to the required concomitant drugs or supportive treatments, was added to ensure subject safety. |
| 11 February 2013 | 1) Since OS was the primary endpoint, the study was amended to remove the requirement of response and progression assessments by an Independent Review Committee and instead to specify that the investigator's assessment of response and progression was to be used. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported