



Clinical trial results:

A PHASE 3, MULTICENTER, RANDOMIZED, OPEN-LABEL STUDY TO COMPARE THE EFFICACY AND SAFETY OF POMALIDOMIDE, BORTEZOMIB AND LOW-DOSE DEXAMETHASONE VERSUS BORTEZOMIB AND LOW-DOSE DEXAMETHASONE IN SUBJECTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA

Summary

| | |
|--------------------------|-------------------------------------|
| EudraCT number | 2014-000268-17 |
| Trial protocol | IE NO DK SE FI ES PT AT PL GR FR IT |
| Global end of trial date | 13 May 2022 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 25 May 2023 |
| First version publication date | 25 May 2023 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | CC-4047-MM-007 |
|-----------------------|----------------|

Additional study identifiers

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

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Bristol-Myers Squibb |
| Sponsor organisation address | Chaussée de la Hulpe 185, Brussels, Belgium, 1170 |
| Public contact | EU Study Start-Up Unit, Bristol-Myers Squibb International Corporation, Clinical.Trials@bms.com |
| Scientific contact | Bristol-Myers Squibb Study Director, Bristol-Myers Squibb, Clinical.Trials@bms.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 | 07 July 2022 |
| Is this the analysis of the primary completion data? | No |

| | |
|----------------------------------|-------------|
| Global end of trial reached? | Yes |
| Global end of trial date | 13 May 2022 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

To compare the efficacy of POM + BTZ + LD-DEX with BTZ + LD-DEX in subjects with relapsed or refractory MM

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization Good Clinical Practice Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 06 December 2016 |
| 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 | Austria: 8 |
| Country: Number of subjects enrolled | Canada: 13 |
| Country: Number of subjects enrolled | Denmark: 8 |
| Country: Number of subjects enrolled | Finland: 5 |
| Country: Number of subjects enrolled | France: 30 |
| Country: Number of subjects enrolled | Germany: 23 |
| Country: Number of subjects enrolled | Greece: 33 |
| Country: Number of subjects enrolled | Ireland: 10 |
| Country: Number of subjects enrolled | Israel: 3 |
| Country: Number of subjects enrolled | Italy: 69 |
| Country: Number of subjects enrolled | Japan: 17 |
| Country: Number of subjects enrolled | Netherlands: 2 |
| Country: Number of subjects enrolled | Norway: 13 |
| Country: Number of subjects enrolled | Poland: 24 |
| Country: Number of subjects enrolled | Portugal: 11 |
| Country: Number of subjects enrolled | Russian Federation: 11 |
| Country: Number of subjects enrolled | Spain: 35 |
| Country: Number of subjects enrolled | Sweden: 9 |
| Country: Number of subjects enrolled | Turkey: 55 |
| Country: Number of subjects enrolled | United Kingdom: 58 |

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United States: 122 |
| Worldwide total number of subjects | 559 |
| EEA total number of subjects | 280 |

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) | 229 |
| From 65 to 84 years | 323 |
| 85 years and over | 7 |

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

548 participants treated

Period 1

| | |
|------------------------------|-------------------------|
| Period 1 title | Randomization |
| Is this the baseline period? | Yes |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-----|
| Are arms mutually exclusive? | Yes |
|------------------------------|-----|

| | |
|------------------|-----------------------------|
| Arm title | Treatment 1: POM+BTZ+LD-DEX |
|------------------|-----------------------------|

Arm description:

POM (Pomalidomide) -4 mg/day on Days 1 to 14 of each 21-day treatment cycle BTZ (Bortezomib) -For Cycles 1 – 8: 1.3 mg/m²/dose on Days 1, 4, 8, and 11 of a 21-day cycle -For Cycles 9 onwards: 1.3 mg/m²/dose on Days 1 and 8 of a 21-day cycle DEX (Dexamethasone) -For Cycles 1 to 8, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle. -For Cycles 9 and onward, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 8, and 9 of a 21-day cycle.

| | |
|--|--------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Bortezomib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Intravascular use , Subcutaneous use |

Dosage and administration details:

For Cycles 1 – 8: 1.3 mg/m²/dose on Days 1, 4, 8, and 11 of a 21-day cycle

For Cycles 9 onwards: 1.3 mg/m²/dose on Days 1 and 8 of a 21-day cycle

The study was initiated using intravenous (IV) BTZ, but was changed to subcutaneous (SC) for both treatment arms in CC-4047-MM-007 Protocol Amendment 1 (dated 27-Mar-2014).

| | |
|--|---------------|
| Investigational medicinal product name | Dexamethasone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

For Cycles 1 to 8, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle.

For Cycles 9 and onward, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 8, and 9 of a 21-day cycle.

| | |
|--|--------------|
| Investigational medicinal product name | pomalidomide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

1 mg, 2 mg, 3 mg, and 4 mg

| | |
|------------------|-------------------------|
| Arm title | Treatment 2: BTZ+LD-DEX |
|------------------|-------------------------|

Arm description:

BTZ ((Bortezomib) -For Cycles 1 – 8: 1.3 mg/m2/dose on Days 1, 4, 8, and 11 of a 21-day cycle -For Cycles 9 onwards: 1.3 mg/m2/dose on Days 1 and 8 of a 21-day cycle DEX (Dexamethasone) -For Cycles 1 to 8, 20 mg/day (\leq 75 years old) or 10 mg/day ($>$ 75 years old) on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle. -For Cycles 9 and onward, 20 mg/day (\leq 75 years old) or 10 mg/day ($>$ 75 years old) on Days 1, 2, 8, and 9 of a 21-day cycle.

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Dexamethasone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

For Cycles 1 to 8, 20 mg/day (\leq 75 years old) or 10 mg/day ($>$ 75 years old) on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle.

For Cycles 9 and onward, 20 mg/day (\leq 75 years old) or 10 mg/day ($>$ 75 years old) on Days 1, 2, 8, and 9 of a 21-day cycle.

| | |
|--|--------------------------------------|
| Investigational medicinal product name | Bortezomib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Intravascular use , Subcutaneous use |

Dosage and administration details:

For Cycles 1 – 8: 1.3 mg/m2/dose on Days 1, 4, 8, and 11 of a 21-day cycle

For Cycles 9 onwards: 1.3 mg/m2/dose on Days 1 and 8 of a 21-day cycle

The study was initiated using intravenous (IV) BTZ, but was changed to subcutaneous (SC) for both treatment arms in CC-4047-MM-007 Protocol Amendment 1 (dated 27-Mar-2014).

| Number of subjects in period 1 | Treatment 1: POM+BTZ+LD-DEX | Treatment 2: BTZ+LD-DEX |
|--------------------------------|--------------------------------|----------------------------|
| Started | 281 | 278 |
| Completed | 278 | 270 |
| Not completed | 3 | 8 |
| Physician decision | - | 1 |
| Consent withdrawn by subject | - | 4 |
| death | 1 | - |
| Progressive Disease | - | 2 |
| Lost to follow-up | 1 | - |
| Randomization Error | 1 | - |
| clinical progression | - | 1 |

Period 2

| | |
|------------------------------|-------------------------|
| Period 2 title | Treatment Period |
| Is this the baseline period? | No |
| Allocation method | Randomised - controlled |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|-----------------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Treatment 1: POM+BTZ+LD-DEX |

Arm description:

POM (Pomalidomide) -4 mg/day on Days 1 to 14 of each 21-day treatment cycle BTZ (Bortezomib) -For Cycles 1 – 8: 1.3 mg/m²/dose on Days 1, 4, 8, and 11 of a 21-day cycle -For Cycles 9 onwards: 1.3 mg/m²/dose on Days 1 and 8 of a 21-day cycle DEX (Dexamethasone) -For Cycles 1 to 8, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle. -For Cycles 9 and onward, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 8, and 9 of a 21-day cycle.

| | |
|--|--------------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Bortezomib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Intravascular use , Subcutaneous use |

Dosage and administration details:

For Cycles 1 – 8: 1.3 mg/m²/dose on Days 1, 4, 8, and 11 of a 21-day cycle

For Cycles 9 onwards: 1.3 mg/m²/dose on Days 1 and 8 of a 21-day cycle

The study was initiated using intravenous (IV) BTZ, but was changed to subcutaneous (SC) for both treatment arms in CC-4047-MM-007 Protocol Amendment 1 (dated 27-Mar-2014).

| | |
|--|---------------|
| Investigational medicinal product name | Dexamethasone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

2 mg and 4 mg

| | |
|--|--------------|
| Investigational medicinal product name | Pomalidomide |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

1 mg, 2 mg, 3 mg, and 4 mg

| | |
|------------------|-------------------------|
| Arm title | Treatment 2: BTZ+LD-DEX |
|------------------|-------------------------|

Arm description:

BTZ ((Bortezomib) -For Cycles 1 – 8: 1.3 mg/m²/dose on Days 1, 4, 8, and 11 of a 21-day cycle -For Cycles 9 onwards: 1.3 mg/m²/dose on Days 1 and 8 of a 21-day cycle DEX (Dexamethasone) -For Cycles 1 to 8, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle. -For Cycles 9 and onward, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 8, and 9 of a 21-day cycle.

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Dexamethasone |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

2 mg and 4 mg

| | |
|--|--------------------------------------|
| Investigational medicinal product name | Bortezomib |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Intravascular use , Subcutaneous use |

Dosage and administration details:

For Cycles 1 – 8: 1.3 mg/m²/dose on Days 1, 4, 8, and 11 of a 21-day cycle

For Cycles 9 onwards: 1.3 mg/m²/dose on Days 1 and 8 of a 21-day cycle

The study was initiated using intravenous (IV) BTZ, but was changed to subcutaneous (SC) for both treatment arms in CC-4047-MM-007 Protocol Amendment 1 (dated 27-Mar-2014).

| Number of subjects in period 2 | Treatment 1: POM+BTZ+LD-DEX | Treatment 2: BTZ+LD-DEX |
|---------------------------------------|--------------------------------|----------------------------|
| Started | 278 | 270 |
| Completed | 0 | 0 |
| Not completed | 278 | 270 |
| Withdrawal of Consent | 25 | 22 |
| Adverse event, serious fatal | 20 | 9 |
| Adverse event, non-fatal | 39 | 52 |
| Other Reasons | 27 | 19 |
| Progressive Disease | 167 | 165 |
| Pregnancy | - | 1 |
| Lost to follow-up | - | 2 |

Baseline characteristics

Reporting groups

| | |
|---|-----------------------------|
| Reporting group title | Treatment 1: POM+BTZ+LD-DEX |
| Reporting group description: | |
| POM (Pomalidomide) -4 mg/day on Days 1 to 14 of each 21-day treatment cycle BTZ (Bortezomib) -For Cycles 1 – 8: 1.3 mg/m2/dose on Days 1, 4, 8, and 11 of a 21-day cycle -For Cycles 9 onwards: 1.3 mg/m2/dose on Days 1 and 8 of a 21-day cycle DEX (Dexamethasone) -For Cycles 1 to 8, 20 mg/day (\leq 75 years old) or 10 mg/day ($>$ 75 years old) on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle. -For Cycles 9 and onward, 20 mg/day (\leq 75 years old) or 10 mg/day ($>$ 75 years old) on Days 1, 2, 8, and 9 of a 21-day cycle. | |
| Reporting group title | Treatment 2: BTZ+LD-DEX |
| Reporting group description: | |
| BTZ ((Bortezomib) -For Cycles 1 – 8: 1.3 mg/m2/dose on Days 1, 4, 8, and 11 of a 21-day cycle -For Cycles 9 onwards: 1.3 mg/m2/dose on Days 1 and 8 of a 21-day cycle DEX (Dexamethasone) -For Cycles 1 to 8, 20 mg/day (\leq 75 years old) or 10 mg/day ($>$ 75 years old) on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle. -For Cycles 9 and onward, 20 mg/day (\leq 75 years old) or 10 mg/day ($>$ 75 years old) on Days 1, 2, 8, and 9 of a 21-day cycle. | |

| Reporting group values | Treatment 1: POM+BTZ+LD-DEX | Treatment 2: BTZ+LD-DEX | Total |
|---|--------------------------------|----------------------------|-------|
| Number of subjects | 281 | 278 | 559 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 114 | 115 | 229 |
| From 65-84 years | 164 | 159 | 323 |
| 85 years and over | 3 | 4 | 7 |
| Age Continuous Units: Years | | | |
| arithmetic mean | 65.9 | 66.1 | |
| standard deviation | \pm 10.13 | \pm 10.16 | - |
| Sex: Female, Male Units: Participants | | | |
| Female | 126 | 131 | 257 |
| Male | 155 | 147 | 302 |
| Race (NIH/OMB) Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | 0 |
| Asian | 14 | 8 | 22 |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | 0 |
| Black or African American | 8 | 13 | 21 |
| White | 237 | 234 | 471 |
| More than one race | 0 | 0 | 0 |
| Unknown or Not Reported | 22 | 23 | 45 |
| Ethnicity (NIH/OMB) Units: Subjects | | | |
| Hispanic or Latino | 17 | 14 | 31 |
| Not Hispanic or Latino | 244 | 241 | 485 |
| Unknown or Not Reported | 20 | 23 | 43 |

End points

End points reporting groups

| | |
|---|-----------------------------|
| Reporting group title | Treatment 1: POM+BTZ+LD-DEX |
| Reporting group description: POM (Pomalidomide) -4 mg/day on Days 1 to 14 of each 21-day treatment cycle BTZ (Bortezomib) -For Cycles 1 – 8: 1.3 mg/m ² /dose on Days 1, 4, 8, and 11 of a 21-day cycle -For Cycles 9 onwards: 1.3 mg/m ² /dose on Days 1 and 8 of a 21-day cycle DEX (Dexamethasone) -For Cycles 1 to 8, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle. -For Cycles 9 and onward, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 8, and 9 of a 21-day cycle. | |
| Reporting group title | Treatment 2: BTZ+LD-DEX |
| Reporting group description: BTZ ((Bortezomib) -For Cycles 1 – 8: 1.3 mg/m ² /dose on Days 1, 4, 8, and 11 of a 21-day cycle -For Cycles 9 onwards: 1.3 mg/m ² /dose on Days 1 and 8 of a 21-day cycle DEX (Dexamethasone) -For Cycles 1 to 8, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle. -For Cycles 9 and onward, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 8, and 9 of a 21-day cycle. | |
| Reporting group title | Treatment 1: POM+BTZ+LD-DEX |
| Reporting group description: POM (Pomalidomide) -4 mg/day on Days 1 to 14 of each 21-day treatment cycle BTZ (Bortezomib) -For Cycles 1 – 8: 1.3 mg/m ² /dose on Days 1, 4, 8, and 11 of a 21-day cycle -For Cycles 9 onwards: 1.3 mg/m ² /dose on Days 1 and 8 of a 21-day cycle DEX (Dexamethasone) -For Cycles 1 to 8, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle. -For Cycles 9 and onward, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 8, and 9 of a 21-day cycle. | |
| Reporting group title | Treatment 2: BTZ+LD-DEX |
| Reporting group description: BTZ ((Bortezomib) -For Cycles 1 – 8: 1.3 mg/m ² /dose on Days 1, 4, 8, and 11 of a 21-day cycle -For Cycles 9 onwards: 1.3 mg/m ² /dose on Days 1 and 8 of a 21-day cycle DEX (Dexamethasone) -For Cycles 1 to 8, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle. -For Cycles 9 and onward, 20 mg/day (≤ 75 years old) or 10 mg/day (> 75 years old) on Days 1, 2, 8, and 9 of a 21-day cycle. | |

Primary: Progression Free Survival by Independent Response Adjudication Committee (IRAC)

| | |
|---|---|
| End point title | Progression Free Survival by Independent Response Adjudication Committee (IRAC) |
| End point description: Progression free survival (PFS) will be calculated as the time between the randomization and progressive disease (PD) or death. Progressive Disease is defined as an Increase of ≥ 25% from nadir in: -Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL)g -Urine M-component and/or (the absolute increase must be ≥ 200 mg/24 hours) -In patients without measurable serum and urine M-protein levels the difference between involved and uninvolved FLC levels, the absolute increase must be > 100 mg/dL. -Bone marrow plasma cell percentage, the absolute % must be ≥ 10%h -Definite development of new bone lesions or soft tissue plasmacytomas increase in the size of existing bone lesions or soft tissue plasmacytomas. -Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder. | |
| End point type | Primary |
| End point timeframe: From randomization to progressive disease or death during the IRAC assessment period, up to approximately 42 months | |

| End point values | Treatment 1: POM+BTZ+LD- DEX | Treatment 2: BTZ+LD-DEX | | |
|----------------------------------|------------------------------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 281 | 278 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 11.20 (9.66 to 13.73) | 7.10 (5.88 to 8.48) | | |

Statistical analyses

| Statistical analysis title | Statistical Analysis for PFS |
|---|---|
| Comparison groups | Treatment 1: POM+BTZ+LD-DEX v Treatment 2: BTZ+LD-DEX |
| Number of subjects included in analysis | 559 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.001 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.61 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.49 |
| upper limit | 0.77 |

Secondary: Overall Survival (OS)

| | |
|------------------------|---|
| End point title | Overall Survival (OS) |
| End point description: | Overall survival (OS) is calculated as the time from randomization to death from any cause. |
| End point type | Secondary |
| End point timeframe: | From randomization to date of death, up to approximately 65 months |

| End point values | Treatment 1: POM+BTZ+LD- DEX | Treatment 2: BTZ+LD-DEX | | |
|----------------------------------|------------------------------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 281 | 278 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 35.58 (28.55 to 41.20) | 31.61 (26.05 to 37.16) | | |

Statistical analyses

| | |
|---|---|
| Statistical analysis title | Statistical Analysis for OS |
| Comparison groups | Treatment 1: POM+BTZ+LD-DEX v Treatment 2: BTZ+LD-DEX |
| Number of subjects included in analysis | 559 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.571 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.94 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.77 |
| upper limit | 1.15 |

Secondary: Overall Response Rate by Independent Response Adjudication Committee (IRAC)

| | |
|-----------------|---|
| End point title | Overall Response Rate by Independent Response Adjudication Committee (IRAC) |
|-----------------|---|

End point description:

The ORR together with the relative proportions in each response category (ie, stringent CR [sCR], CR, very good PR [VGPR], PR, SD, and PD) by treatment using the IMWG criteria will be examined.

Complete Response: Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and $\leq 5\%$ plasma cells in bone marrow

SCR: CR+ Normal FLC ratio and Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence

VGPR: Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine Mprotein level < 100 mg per 24 hours

PR: $\geq 50\%$ reduction of serum M-Protein and reduction in 24-hour urinary M-protein by $\geq 90\%$ or to < 200 mg per 24 hours

Progressive Disease: Please refer to Primary outcome measure for definition

SD: Not meeting criteria for CR, VGPR, PR, or progressive disease

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

End point timeframe:

From randomization to progressive disease or death during the IRAC assessment period, up to approximately 42 months

| End point values | Treatment 1: POM+BTZ+LD- DEX | Treatment 2: BTZ+LD-DEX | | |
|-----------------------------|------------------------------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 281 | 278 | | |
| Units: Participants | | | | |
| Stringent Complete Response | 9 | 2 | | |
| Complete Response | 35 | 9 | | |
| Very Good Partial Response | 104 | 40 | | |
| Partial Response | 83 | 88 | | |
| Stable Disease | 32 | 106 | | |
| Progressive Disease | 11 | 16 | | |
| Not Evaluable | 7 | 17 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response by Independent Response Adjudication Committee (IRAC)

| | |
|-----------------|--|
| End point title | Duration of Response by Independent Response Adjudication Committee (IRAC) |
|-----------------|--|

End point description:

Duration of myeloma response is defined as the duration from the time when the IMWG response criteria are first met for sCR or CR or VGPR or PR until the first date the response criteria are met for PD or until the subject died from any cause, whichever occurs first.

Complete Response: Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and $\leq 5\%$ plasma cells in bone marrow

SCR: CR+ Normal FLC ratio and Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence

VGPR: Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine Mprotein level < 100 mg per 24 hours

PR: $\geq 50\%$ reduction of serum M-Protein and reduction in 24-hour urinary M-protein by $\geq 90\%$ or to < 200 mg per 24 hours

Progressive Disease: Please refer to Primary outcome measure for definition

SD: Not meeting criteria for CR, VGPR, PR, or progressive disease

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

End point timeframe:

From randomization to progressive disease or death during the IRAC assessment period, up to approximately 42 months

| End point values | Treatment 1: POM+BTZ+LD- DEX | Treatment 2: BTZ+LD-DEX | | |
|----------------------------------|------------------------------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 231 | 139 | | |
| Units: Months | | | | |
| median (confidence interval 95%) | 13.70 (10.94 to 18.10) | 10.94 (8.11 to 14.78) | | |

Statistical analyses

| Statistical analysis title | Statistical Analysis for DOR |
|---|---|
| Comparison groups | Treatment 1: POM+BTZ+LD-DEX v Treatment 2: BTZ+LD-DEX |
| Number of subjects included in analysis | 370 |
| Analysis specification | Pre-specified |
| Analysis type | |
| P-value | = 0.064 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.76 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.56 |
| upper limit | 1.02 |

Secondary: Number of Participants with grade 3-4 Treatment Emergent Adverse Events (TEAE)

| | |
|------------------------|--|
| End point title | Number of Participants with grade 3-4 Treatment Emergent Adverse Events (TEAE) |
| End point description: | Treatment-emergent adverse events (TEAEs) are defined as any AE occurring or worsening on or after the first dose date of the study treatment and within 28 days after the last dose date. |
| End point type | Secondary |
| End point timeframe: | From first dose to 28 days after the last dose (up to approximately 44 months) |

| End point values | Treatment 1: POM+BTZ+LD- DEX | Treatment 2: BTZ+LD-DEX | | |
|-----------------------------|------------------------------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 278 | 270 | | |
| Units: Participants | 259 | 194 | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with grade 5 Treatment Emergent Adverse Events (TEAE)

| | |
|-----------------|--|
| End point title | Number of Participants with grade 5 Treatment Emergent Adverse Events (TEAE) |
|-----------------|--|

End point description:

Treatment-emergent adverse events (TEAEs) are defined as any AE occurring or worsening on or after the first dose date of the study treatment and within 28 days after the last dose date.

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

End point timeframe:

From first dose to 28 days after the last dose (up to approximately 44 months)

| End point values | Treatment 1: POM+BTZ+LD- DEX | Treatment 2: BTZ+LD-DEX | | |
|-----------------------------|------------------------------------|----------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 278 | 270 | | |
| Units: Participants | 29 | 12 | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AEs and SAEs: From first treatment to 28 days after last dose, up to approximately 44 months on average of 10 months.

All-Cause mortality: from randomization to end of the study, approximately 65 months.

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

Dictionary used

| | |
|--------------------|--------|
| Dictionary name | MedDRA |
| Dictionary version | 20.0 |

Reporting groups

| | |
|-----------------------|--------------|
| Reporting group title | BTZ + LD-DEX |
|-----------------------|--------------|

Reporting group description:

BTZ ((Bortezomib) -For Cycles 1 – 8: 1.3 mg/m2/dose on Days 1, 4, 8, and 11 of a 21-day cycle -For Cycles 9 onwards: 1.3 mg/m2/dose on Days 1 and 8 of a 21-day cycle DEX (Dexamethasone) -For Cycles 1 to 8, 20 mg/day (\leq 75 years old) or 10 mg/day ($>$ 75 years old) on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle. -For Cycles 9 and onward, 20 mg/day (\leq 75 years old) or 10 mg/day ($>$ 75 years old) on Days 1, 2, 8, and 9 of a 21-day cycle.

| | |
|-----------------------|--------------------|
| Reporting group title | POM + BTZ + LD-DEX |
|-----------------------|--------------------|

Reporting group description:

POM (Pomalidomide) -4 mg/day on Days 1 to 14 of each 21-day treatment cycle BTZ (Bortezomib) -For Cycles 1 – 8: 1.3 mg/m2/dose on Days 1, 4, 8, and 11 of a 21-day cycle -For Cycles 9 onwards: 1.3 mg/m2/dose on Days 1 and 8 of a 21-day cycle DEX (Dexamethasone) -For Cycles 1 to 8, 20 mg/day (\leq 75 years old) or 10 mg/day ($>$ 75 years old) on Days 1, 2, 4, 5, 8, 9, 11 and 12 of a 21-day cycle. -For Cycles 9 and onward, 20 mg/day (\leq 75 years old) or 10 mg/day ($>$ 75 years old) on Days 1, 2, 8, and 9 of a 21-day cycle.

| Serious adverse events | BTZ + LD-DEX | POM + BTZ + LD-DEX | |
|---|--------------------|--------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 119 / 270 (44.07%) | 177 / 278 (63.67%) | |
| number of deaths (all causes) | 190 | 196 | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Bronchial carcinoma | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute lymphocytic leukaemia | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| 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 | 1 / 270 (0.37%) | 6 / 278 (2.16%) | |
| occurrences causally related to treatment / all | 0 / 1 | 4 / 12 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Basosquamous carcinoma | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bowen's disease | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 2 / 278 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Keratoacanthoma | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Plasma cell leukaemia | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Plasmacytoma | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Porocarcinoma | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Prostate cancer | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal cell carcinoma | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Scrotal cancer | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 2 / 270 (0.74%) | 4 / 278 (1.44%) | |
| occurrences causally related to treatment / all | 0 / 2 | 2 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metastases to meninges | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vascular disorders | | | |
| Peripheral arterial occlusive disease | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 4 / 270 (1.48%) | 4 / 278 (1.44%) | |
| occurrences causally related to treatment / all | 1 / 4 | 4 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypertension | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypotension | | | |

| | | | |
|--|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 270 (0.37%) | 3 / 278 (1.08%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Orthostatic hypotension | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Circulatory collapse | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pregnancy, puerperium and perinatal conditions | | | |
| Pregnancy | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (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 | | | |
| General physical health deterioration | | | |
| subjects affected / exposed | 9 / 270 (3.33%) | 5 / 278 (1.80%) | |
| occurrences causally related to treatment / all | 1 / 10 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 4 | 0 / 4 | |
| Death | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 4 / 278 (1.44%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 2 / 4 | |
| Fatigue | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gait disturbance | | | |
| subjects affected / exposed | 2 / 270 (0.74%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|------------------|--|
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 2 / 270 (0.74%) | 3 / 278 (1.08%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pain | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pyrexia | | | |
| subjects affected / exposed | 5 / 270 (1.85%) | 12 / 278 (4.32%) | |
| occurrences causally related to treatment / all | 2 / 5 | 7 / 13 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Systemic inflammatory response syndrome | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malaise | | | |
| subjects affected / exposed | 2 / 270 (0.74%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Respiratory acidosis | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Acute respiratory failure | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 3 / 278 (1.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 4 / 278 (1.44%) | |
| occurrences causally related to treatment / all | 0 / 1 | 3 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Haemothorax | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoxia | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 2 / 278 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pleural effusion | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 3 / 270 (1.11%) | 3 / 278 (1.08%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (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 / 270 (0.37%) | 9 / 278 (3.24%) | |
| occurrences causally related to treatment / all | 0 / 1 | 8 / 9 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory alkalosis | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory failure | | | |
| subjects affected / exposed | 2 / 270 (0.74%) | 2 / 278 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Confusional state | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depression | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mental status changes | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Investigations | | | |
| Coronavirus test positive | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aspartate aminotransferase increased | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood alkaline phosphatase increased | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Chest X-ray abnormal | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| General physical condition abnormal | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutrophil count decreased | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| International normalised ratio increased | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Injury, poisoning and procedural complications | | | |
| Cervical vertebral fracture | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Head injury | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Humerus fracture | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 2 / 278 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infusion related reaction | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Overdose | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Post procedural haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (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 | 1 / 270 (0.37%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal fracture | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Subcutaneous haematoma | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Femur fracture | | | |
| subjects affected / exposed | 3 / 270 (1.11%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac disorders | | | |
| Bundle branch block left | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute coronary syndrome | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 2 / 278 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina pectoris | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Angina unstable | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 2 / 278 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 270 (0.74%) | 9 / 278 (3.24%) | |
| occurrences causally related to treatment / all | 0 / 2 | 7 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 2 / 278 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrial thrombosis | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block complete | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Atrioventricular block second degree | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bradycardia | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac arrest | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 270 (0.00%) | 2 / 278 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 2 | |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 2 / 270 (0.74%) | 3 / 278 (1.08%) | |
| occurrences causally related to treatment / all | 2 / 3 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Coronary artery disease | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 2 / 278 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Left ventricular dysfunction | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Left ventricular failure | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Pericardial effusion | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pericarditis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Restrictive cardiomyopathy | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinus bradycardia | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sinus node dysfunction | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 2 / 278 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cardiac failure | | | |
| subjects affected / exposed | 2 / 270 (0.74%) | 3 / 278 (1.08%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nervous system disorders | | | |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 2 / 278 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Altered state of consciousness | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Amnesia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Aphasia | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Dizziness | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Disturbance in attention | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epilepsy | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Generalised tonic-clonic seizure | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Guillain-Barre syndrome | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatic encephalopathy | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | |
| Hypoxic-ischaemic encephalopathy | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic cerebral infarction | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ischaemic stroke | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Loss of consciousness | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lumbar radiculopathy | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Motor dysfunction | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nerve root compression | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paraparesis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cognitive disorder | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Depressed level of consciousness | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Paraplegia | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Presyncope | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal cord compression | | | |
| subjects affected / exposed | 2 / 270 (0.74%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Syncope | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 5 / 270 (1.85%) | 6 / 278 (2.16%) | |
| occurrences causally related to treatment / all | 0 / 5 | 4 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Trigeminal neuralgia | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Peripheral motor neuropathy | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Blood and lymphatic system disorders | | | |
| Febrile neutropenia | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 5 / 278 (1.80%) | |
| occurrences causally related to treatment / all | 1 / 1 | 5 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Anaemia | | | |
| subjects affected / exposed | 5 / 270 (1.85%) | 4 / 278 (1.44%) | |
| occurrences causally related to treatment / all | 1 / 5 | 1 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Hyperviscosity syndrome | | | |
| subjects affected / exposed | 3 / 270 (1.11%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Neutropenia | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Thrombocytopenia | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 3 / 270 (1.11%) | 2 / 278 (0.72%) | |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lymphopenia | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinal vein thrombosis | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retinal detachment | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal disorders | | | |
| Haemorrhoidal haemorrhage | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 2 / 278 (0.72%) | |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Abdominal pain upper | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 2 / 278 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Colonic fistula | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| 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 / 270 (0.74%) | 2 / 278 (0.72%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diarrhoea | | | |
| subjects affected / exposed | 6 / 270 (2.22%) | 5 / 278 (1.80%) | |
| occurrences causally related to treatment / all | 6 / 9 | 4 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Enterocolitis | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Food poisoning | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric haemorrhage | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric ulcer haemorrhage | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastric volvulus | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Ileus | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Lower gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (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 / 270 (1.11%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 1 / 4 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pancreatitis acute | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Parotid gland enlargement | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retroperitoneal haematoma | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Retroperitoneal haemorrhage | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Umbilical hernia | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Vomiting | | | |
| subjects affected / exposed | 3 / 270 (1.11%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 1 / 5 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Intestinal obstruction | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cholecystitis chronic | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatitis acute | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hepatotoxicity | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperbilirubinaemia | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin disorder | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal and urinary disorders | | | |
| Chronic kidney disease | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute kidney injury | | | |
| subjects affected / exposed | 6 / 270 (2.22%) | 8 / 278 (2.88%) | |
| occurrences causally related to treatment / all | 0 / 7 | 1 / 8 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Anuria | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Nephrolithiasis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary bladder haemorrhage | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary retention | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Renal colic | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocrine disorders | | | |
| Hyperthyroidism | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Arthritis | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bone pain | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |

| | | | |
|---|-----------------|-----------------|--|
| Cervical spinal stenosis | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (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 | 1 / 270 (0.37%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteorrhagia | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Pain in extremity | | | |
| subjects affected / exposed | 2 / 270 (0.74%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pathological fracture | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 2 / 278 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Spinal pain | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Back pain | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 270 (0.37%) | 3 / 278 (1.08%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |
| Atypical pneumonia | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Abscess limb | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Acute hepatitis B | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bacterial sepsis | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchiolitis | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis | | | |
| subjects affected / exposed | 2 / 270 (0.74%) | 3 / 278 (1.08%) | |
| occurrences causally related to treatment / all | 0 / 2 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis bacterial | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchitis pneumococcal | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Catheter site infection | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 2 / 278 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Clostridium difficile colitis | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 4 / 278 (1.44%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Clostridium difficile infection | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Device related infection | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Bronchopulmonary aspergillosis | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Endocarditis | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Influenza | | | |
| subjects affected / exposed | 4 / 270 (1.48%) | 10 / 278 (3.60%) | |
| occurrences causally related to treatment / all | 0 / 4 | 5 / 11 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Enterococcal sepsis | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Epididymitis | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Erysipelas | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 2 / 278 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia bacteraemia | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Escherichia sepsis | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | |
| Escherichia urinary tract infection | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 3 / 278 (1.08%) | |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Gastroenteritis salmonella | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 2 / 278 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| H1N1 influenza | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Haemophilus infection | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes oesophagitis | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Herpes zoster | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hordeolum | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infection | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 3 / 278 (1.08%) | |
| occurrences causally related to treatment / all | 0 / 1 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Enterobacter pneumonia | | | |

| | | | |
|---|-----------------|------------------|--|
| subjects affected / exposed | 1 / 270 (0.37%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Leishmaniasis | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Localised infection | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (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 | 5 / 270 (1.85%) | 10 / 278 (3.60%) | |
| occurrences causally related to treatment / all | 3 / 6 | 2 / 11 | |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | |
| Lung infection | | | |
| subjects affected / exposed | 2 / 270 (0.74%) | 2 / 278 (0.72%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Mastoiditis | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningitis listeria | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Meningococcal infection | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Muscle abscess | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Oesophageal candidiasis | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Osteomyelitis | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Periorbital cellulitis | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngitis | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pharyngotonsillitis | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumococcal sepsis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia haemophilus | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection bacterial | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia legionella | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 2 / 278 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia moraxella | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia parainfluenzae viral | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia pneumococcal | | | |
| subjects affected / exposed | 2 / 270 (0.74%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia respiratory syncytial viral | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia staphylococcal | | | |

| | | | |
|---|------------------|-------------------|--|
| subjects affected / exposed | 0 / 270 (0.00%) | 2 / 278 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | |
| Pneumonia streptococcal | | | |
| subjects affected / exposed | 2 / 270 (0.74%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pulmonary sepsis | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 2 / 278 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory syncytial virus bronchiolitis | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia | | | |
| subjects affected / exposed | 17 / 270 (6.30%) | 34 / 278 (12.23%) | |
| occurrences causally related to treatment / all | 15 / 23 | 19 / 45 | |
| deaths causally related to treatment / all | 1 / 1 | 1 / 1 | |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 2 / 278 (0.72%) | |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory syncytial virus infection | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 2 / 278 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 5 / 278 (1.80%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Pneumonia influenzal | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 0 / 270 (0.00%) | 2 / 278 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Respiratory tract infection viral | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Rhinovirus infection | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Sepsis | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 5 / 278 (1.80%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 5 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Septic shock | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 6 / 278 (2.16%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 6 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 2 | |
| Sinusitis | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 2 / 278 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Skin infection | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 2 / 278 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal bacteraemia | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal sepsis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 270 (0.37%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Streptococcal sepsis | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 3 / 270 (1.11%) | 3 / 278 (1.08%) | |
| occurrences causally related to treatment / all | 0 / 3 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 3 / 278 (1.08%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 4 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection bacterial | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urinary tract infection staphylococcal | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Urosepsis | | | |
| subjects affected / exposed | 2 / 270 (0.74%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 1 / 2 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 2 / 270 (0.74%) | 3 / 278 (1.08%) | |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Diabetes mellitus | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypercalcaemia | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 3 / 278 (1.08%) | |
| occurrences causally related to treatment / all | 1 / 1 | 3 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypoalbuminaemia | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 2 / 278 (0.72%) | |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 3 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hypovolaemia | | | |
| subjects affected / exposed | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Malnutrition | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolic acidosis | | | |

| | | | |
|---|-----------------|-----------------|--|
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (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 | 0 / 270 (0.00%) | 1 / 278 (0.36%) | |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Type 2 diabetes mellitus | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 0 / 278 (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 | BTZ + LD-DEX | POM + BTZ + LD-DEX | |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 260 / 270 (96.30%) | 276 / 278 (99.28%) | |
| Vascular disorders | | | |
| Hypotension | | | |
| subjects affected / exposed | 13 / 270 (4.81%) | 26 / 278 (9.35%) | |
| occurrences (all) | 16 | 34 | |
| Hypertension | | | |
| subjects affected / exposed | 22 / 270 (8.15%) | 24 / 278 (8.63%) | |
| occurrences (all) | 26 | 32 | |
| General disorders and administration site conditions | | | |
| Pyrexia | | | |
| subjects affected / exposed | 33 / 270 (12.22%) | 72 / 278 (25.90%) | |
| occurrences (all) | 43 | 110 | |
| Oedema peripheral | | | |
| subjects affected / exposed | 54 / 270 (20.00%) | 101 / 278 (36.33%) | |
| occurrences (all) | 60 | 124 | |
| Influenza like illness | | | |
| subjects affected / exposed | 9 / 270 (3.33%) | 15 / 278 (5.40%) | |
| occurrences (all) | 19 | 23 | |
| Fatigue | | | |

| | | | |
|---|-------------------|--------------------|--|
| subjects affected / exposed | 72 / 270 (26.67%) | 107 / 278 (38.49%) | |
| occurrences (all) | 84 | 129 | |
| Asthenia | | | |
| subjects affected / exposed | 48 / 270 (17.78%) | 52 / 278 (18.71%) | |
| occurrences (all) | 65 | 85 | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 45 / 270 (16.67%) | 66 / 278 (23.74%) | |
| occurrences (all) | 64 | 101 | |
| Dyspnoea | | | |
| subjects affected / exposed | 32 / 270 (11.85%) | 62 / 278 (22.30%) | |
| occurrences (all) | 35 | 85 | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 16 / 270 (5.93%) | 17 / 278 (6.12%) | |
| occurrences (all) | 21 | 18 | |
| Productive cough | | | |
| subjects affected / exposed | 13 / 270 (4.81%) | 17 / 278 (6.12%) | |
| occurrences (all) | 17 | 21 | |
| Psychiatric disorders | | | |
| Anxiety | | | |
| subjects affected / exposed | 17 / 270 (6.30%) | 13 / 278 (4.68%) | |
| occurrences (all) | 19 | 15 | |
| Depression | | | |
| subjects affected / exposed | 7 / 270 (2.59%) | 16 / 278 (5.76%) | |
| occurrences (all) | 7 | 16 | |
| Insomnia | | | |
| subjects affected / exposed | 54 / 270 (20.00%) | 49 / 278 (17.63%) | |
| occurrences (all) | 61 | 61 | |
| Investigations | | | |
| Alanine aminotransferase increased | | | |
| subjects affected / exposed | 3 / 270 (1.11%) | 14 / 278 (5.04%) | |
| occurrences (all) | 3 | 21 | |
| Weight decreased | | | |
| subjects affected / exposed | 18 / 270 (6.67%) | 20 / 278 (7.19%) | |
| occurrences (all) | 18 | 21 | |
| Weight increased | | | |

| | | | |
|--|------------------------|------------------------|--|
| subjects affected / exposed occurrences (all) | 19 / 270 (7.04%) 22 | 19 / 278 (6.83%) 26 | |
| Injury, poisoning and procedural complications | | | |
| Accidental overdose | | | |
| subjects affected / exposed | 11 / 270 (4.07%) | 35 / 278 (12.59%) | |
| occurrences (all) | 20 | 71 | |
| Fall | | | |
| subjects affected / exposed | 11 / 270 (4.07%) | 20 / 278 (7.19%) | |
| occurrences (all) | 19 | 38 | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 5 / 270 (1.85%) | 26 / 278 (9.35%) | |
| occurrences (all) | 5 | 31 | |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 29 / 270 (10.74%) | 49 / 278 (17.63%) | |
| occurrences (all) | 36 | 66 | |
| Dysgeusia | | | |
| subjects affected / exposed | 8 / 270 (2.96%) | 18 / 278 (6.47%) | |
| occurrences (all) | 8 | 19 | |
| Headache | | | |
| subjects affected / exposed | 25 / 270 (9.26%) | 35 / 278 (12.59%) | |
| occurrences (all) | 36 | 52 | |
| Hypoaesthesia | | | |
| subjects affected / exposed | 15 / 270 (5.56%) | 7 / 278 (2.52%) | |
| occurrences (all) | 15 | 7 | |
| Paraesthesia | | | |
| subjects affected / exposed | 5 / 270 (1.85%) | 18 / 278 (6.47%) | |
| occurrences (all) | 5 | 22 | |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 103 / 270 (38.15%) | 133 / 278 (47.84%) | |
| occurrences (all) | 133 | 197 | |
| Syncope | | | |
| subjects affected / exposed | 6 / 270 (2.22%) | 14 / 278 (5.04%) | |
| occurrences (all) | 7 | 16 | |
| Tremor | | | |

| | | | |
|--------------------------------------|--------------------|--------------------|--|
| subjects affected / exposed | 8 / 270 (2.96%) | 32 / 278 (11.51%) | |
| occurrences (all) | 9 | 36 | |
| Peripheral sensorimotor neuropathy | | | |
| subjects affected / exposed | 12 / 270 (4.44%) | 18 / 278 (6.47%) | |
| occurrences (all) | 13 | 20 | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 72 / 270 (26.67%) | 87 / 278 (31.29%) | |
| occurrences (all) | 111 | 142 | |
| Leukopenia | | | |
| subjects affected / exposed | 9 / 270 (3.33%) | 37 / 278 (13.31%) | |
| occurrences (all) | 10 | 87 | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 105 / 270 (38.89%) | 110 / 278 (39.57%) | |
| occurrences (all) | 178 | 196 | |
| Neutropenia | | | |
| subjects affected / exposed | 29 / 270 (10.74%) | 150 / 278 (53.96%) | |
| occurrences (all) | 45 | 575 | |
| Lymphopenia | | | |
| subjects affected / exposed | 9 / 270 (3.33%) | 14 / 278 (5.04%) | |
| occurrences (all) | 34 | 41 | |
| Eye disorders | | | |
| Vision blurred | | | |
| subjects affected / exposed | 9 / 270 (3.33%) | 14 / 278 (5.04%) | |
| occurrences (all) | 9 | 14 | |
| Cataract | | | |
| subjects affected / exposed | 3 / 270 (1.11%) | 22 / 278 (7.91%) | |
| occurrences (all) | 3 | 26 | |
| Gastrointestinal disorders | | | |
| Dyspepsia | | | |
| subjects affected / exposed | 25 / 270 (9.26%) | 22 / 278 (7.91%) | |
| occurrences (all) | 25 | 24 | |
| Dry mouth | | | |
| subjects affected / exposed | 11 / 270 (4.07%) | 19 / 278 (6.83%) | |
| occurrences (all) | 11 | 21 | |
| Diarrhoea | | | |

| | | | |
|---|-------------------|--------------------|--|
| subjects affected / exposed | 82 / 270 (30.37%) | 102 / 278 (36.69%) | |
| occurrences (all) | 137 | 202 | |
| Constipation | | | |
| subjects affected / exposed | 65 / 270 (24.07%) | 106 / 278 (38.13%) | |
| occurrences (all) | 81 | 158 | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 16 / 270 (5.93%) | 23 / 278 (8.27%) | |
| occurrences (all) | 18 | 28 | |
| Abdominal pain | | | |
| subjects affected / exposed | 19 / 270 (7.04%) | 30 / 278 (10.79%) | |
| occurrences (all) | 20 | 41 | |
| Abdominal distension | | | |
| subjects affected / exposed | 6 / 270 (2.22%) | 17 / 278 (6.12%) | |
| occurrences (all) | 6 | 19 | |
| Nausea | | | |
| subjects affected / exposed | 56 / 270 (20.74%) | 52 / 278 (18.71%) | |
| occurrences (all) | 67 | 75 | |
| Vomiting | | | |
| subjects affected / exposed | 27 / 270 (10.00%) | 35 / 278 (12.59%) | |
| occurrences (all) | 41 | 49 | |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 270 (0.37%) | 17 / 278 (6.12%) | |
| occurrences (all) | 1 | 20 | |
| Skin and subcutaneous tissue disorders | | | |
| Rash | | | |
| subjects affected / exposed | 11 / 270 (4.07%) | 31 / 278 (11.15%) | |
| occurrences (all) | 11 | 36 | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 32 / 270 (11.85%) | 39 / 278 (14.03%) | |
| occurrences (all) | 36 | 52 | |
| Back pain | | | |
| subjects affected / exposed | 38 / 270 (14.07%) | 61 / 278 (21.94%) | |
| occurrences (all) | 41 | 84 | |
| Bone pain | | | |

| | | | |
|---|-------------------|-------------------|--|
| subjects affected / exposed | 14 / 270 (5.19%) | 25 / 278 (8.99%) | |
| occurrences (all) | 15 | 33 | |
| Muscle spasms | | | |
| subjects affected / exposed | 16 / 270 (5.93%) | 30 / 278 (10.79%) | |
| occurrences (all) | 17 | 39 | |
| Muscular weakness | | | |
| subjects affected / exposed | 12 / 270 (4.44%) | 41 / 278 (14.75%) | |
| occurrences (all) | 14 | 44 | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 17 / 270 (6.30%) | 23 / 278 (8.27%) | |
| occurrences (all) | 21 | 24 | |
| Myalgia | | | |
| subjects affected / exposed | 11 / 270 (4.07%) | 15 / 278 (5.40%) | |
| occurrences (all) | 12 | 16 | |
| Pain in extremity | | | |
| subjects affected / exposed | 38 / 270 (14.07%) | 42 / 278 (15.11%) | |
| occurrences (all) | 44 | 47 | |
| Infections and infestations | | | |
| Viral upper respiratory tract infection | | | |
| subjects affected / exposed | 18 / 270 (6.67%) | 36 / 278 (12.95%) | |
| occurrences (all) | 21 | 80 | |
| Urinary tract infection | | | |
| subjects affected / exposed | 28 / 270 (10.37%) | 36 / 278 (12.95%) | |
| occurrences (all) | 42 | 76 | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 51 / 270 (18.89%) | 71 / 278 (25.54%) | |
| occurrences (all) | 79 | 156 | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 16 / 270 (5.93%) | 21 / 278 (7.55%) | |
| occurrences (all) | 17 | 33 | |
| Pneumonia | | | |
| subjects affected / exposed | 21 / 270 (7.78%) | 26 / 278 (9.35%) | |
| occurrences (all) | 26 | 30 | |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 8 / 270 (2.96%) | 17 / 278 (6.12%) | |
| occurrences (all) | 9 | 40 | |

| | | | |
|------------------------------------|-------------------|-------------------|--|
| Influenza | | | |
| subjects affected / exposed | 13 / 270 (4.81%) | 27 / 278 (9.71%) | |
| occurrences (all) | 14 | 44 | |
| Conjunctivitis | | | |
| subjects affected / exposed | 16 / 270 (5.93%) | 26 / 278 (9.35%) | |
| occurrences (all) | 19 | 36 | |
| Bronchitis | | | |
| subjects affected / exposed | 20 / 270 (7.41%) | 43 / 278 (15.47%) | |
| occurrences (all) | 30 | 66 | |
| Metabolism and nutrition disorders | | | |
| Decreased appetite | | | |
| subjects affected / exposed | 26 / 270 (9.63%) | 29 / 278 (10.43%) | |
| occurrences (all) | 28 | 31 | |
| Hyperglycaemia | | | |
| subjects affected / exposed | 28 / 270 (10.37%) | 43 / 278 (15.47%) | |
| occurrences (all) | 48 | 82 | |
| Hypocalcaemia | | | |
| subjects affected / exposed | 10 / 270 (3.70%) | 20 / 278 (7.19%) | |
| occurrences (all) | 11 | 42 | |
| Hypokalaemia | | | |
| subjects affected / exposed | 31 / 270 (11.48%) | 45 / 278 (16.19%) | |
| occurrences (all) | 51 | 81 | |
| Hypomagnesaemia | | | |
| subjects affected / exposed | 7 / 270 (2.59%) | 20 / 278 (7.19%) | |
| occurrences (all) | 9 | 23 | |
| Hypophosphataemia | | | |
| subjects affected / exposed | 10 / 270 (3.70%) | 20 / 278 (7.19%) | |
| occurrences (all) | 21 | 39 | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 03 February 2014 | -Updated route of administration for the bortezomib in both treatment arms to subcutaneous from intravenous-Added quality of life assessment to allow an exploratory evaluation of the differences in health-related quality of life- Added biomarker sampling to allow for an exploratory evaluation of Minimal Residue Disease (MRD), genomic, molecular/mechanistic and immune biomarkers and their correlation to clinical outcome measures-Added an endpoint to allow for an exploratory evaluation of the Progression-free survival after next-line therapy (PFS2) |
| 14 November 2014 | The main purpose of this protocol amendment is to allow for the expansion of trial enrollment to countries and sites outside of the US in order to aid in completing enrollment. The changes outlined throughout this document are required in order to expand globally; including updates to the Investigational Product sections and the collection of both Exploratory Biomarker samples and Quality of Life information. |
| 16 October 2015 | Approval status of Pomalyst in the United States has been updated following full approval notification on 23 April 2015 Reduction in overall sample sizeUpdates to time points for contraceptive requirements and pregnancy testing |
| 09 December 2015 | Revision in overall sample size Updated Sections: Protocol Summary, Section 4.1, Section 7.1, Section 10.3, Section 10.9, Section 10.10 |
| 14 June 2017 | Perform the final PFS analysis before the originally planned PFS events (381) are reached -Updated statistical considerations for the study will be specified in the protocol amendment and revised statistical analysis plan (SAP). |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported