



Clinical trial results:

A Phase 3, Multicenter, Randomized, Open-label Study to Compare the Efficacy and Safety of Pomalidomide in Combination with Low-Dose Dexamethasone versus High-Dose Dexamethasone in Subjects with Refractory or Relapsed and Refractory Multiple Myeloma

Summary

| | |
|--------------------------|-------------------------------|
| EudraCT number | 2010-019820-30 |
| Trial protocol | BE GB DE GR IT CZ NL ES SE DK |
| Global end of trial date | 28 August 2017 |

Results information

| | |
|--------------------------------|-------------------|
| Result version number | v1 (current) |
| This version publication date | 08 September 2018 |
| First version publication date | 08 September 2018 |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | CC-4047-MM-003 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01311687 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Celgene Corporation |
| Sponsor organisation address | 86 Morris Avenue, Summit, NJ, United States, 07901 |
| Public contact | Clinical Trial Disclosure, Celgene Corporation, ClinicalTrialDisclosure@celgene.com |
| Scientific contact | Lars Sternas, Celgene Corporation, +1 908 6739301, LSternas@Celgene.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 | 28 August 2017 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 28 August 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to compare the efficacy of pomalidomide + low-dose dexamethasone (LD-dex) with that of high-dose dexamethasone (HD-dex) in subjects with refractory multiple myeloma (MM) or relapsed and refractory MM.

Protection of trial subjects:

This study was conducted in accordance with the guidelines of current Good Clinical Practice including the archiving of essential documents.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 18 March 2011 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Efficacy, Safety |
| Long term follow-up duration | 5 Years |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-----------------------|
| Country: Number of subjects enrolled | Switzerland: 16 |
| Country: Number of subjects enrolled | Germany: 69 |
| Country: Number of subjects enrolled | Denmark: 10 |
| Country: Number of subjects enrolled | Spain: 50 |
| Country: Number of subjects enrolled | France: 74 |
| Country: Number of subjects enrolled | United Kingdom: 40 |
| Country: Number of subjects enrolled | Greece: 31 |
| Country: Number of subjects enrolled | Italy: 40 |
| Country: Number of subjects enrolled | Netherlands: 9 |
| Country: Number of subjects enrolled | Russian Federation: 9 |
| Country: Number of subjects enrolled | Sweden: 6 |
| Country: Number of subjects enrolled | United States: 3 |
| Country: Number of subjects enrolled | Australia: 22 |
| Country: Number of subjects enrolled | Belgium: 24 |
| Country: Number of subjects enrolled | Canada: 52 |
| Worldwide total number of subjects | 455 |
| EEA total number of subjects | 353 |

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) | 232 |
| From 65 to 84 years | 222 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 93 sites: 68 sites in Europe, 10 sites in Australia, 10 sites in Canada, 4 sites in Russia, and 1 site in the United States (US) from 18 March 2011 to 29 August 2017.

Pre-assignment

Screening details:

Participants were randomized in a 2:1 ratio. Treatment phase discontinuation occurred when a participant had confirmed progressive disease. Participants who did not progress but who were intolerant to treatment, or no longer wished to receive study treatment entered the progression-free survival (PFS) follow-up period until disease progression.

Period 1

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

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Pomalidomide plus Low-Dose Dexamethasone |

Arm description:

Participants received 4 mg pomalidomide administered by mouth on Days 1-21 of each 28-day treatment cycle and 40 mg dexamethasone (participants > 75 years of age received 20 mg dexamethasone) administered by mouth once per day on Days 1, 8, 15, and 22 of a 28-day cycle until disease progression.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Pomalidomide |
| Investigational medicinal product code | CC-4047 |
| Other name | Pomalyst® |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

4 mg pomalidomide capsules administered orally on Days 1-21 of each 28-day treatment cycle.

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

Dosage and administration details:

40 mg dexamethasone (or 20 mg for participants > 75 years of age) tablets administered orally Days 1, 8, 15, and 22 of each 28-day treatment cycle.

| | |
|------------------|-------------------------|
| Arm title | High-Dose Dexamethasone |
|------------------|-------------------------|

Arm description:

Participants received 40 mg dexamethasone (participants > 75 years of age received 20 mg dexamethasone) administered by mouth once per day on Days 1 through 4, 9 through 12, and 17 through 20 of a 28-day cycle until disease progression.

| | |
|----------|-------------------|
| Arm type | Active comparator |
|----------|-------------------|

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

Dosage and administration details:

40 mg dexamethasone (or 20 mg for participants > 75 years of age) tablets administered orally on Days 1 to 4, 9 to 12, and 17 to 20 of each 28-day treatment cycle.

| Number of subjects in period 1 | Pomalidomide plus Low-Dose Dexamethasone | High-Dose Dexamethasone |
|--------------------------------|--|-------------------------|
| Started | 302 | 153 |
| Received Study Drug | 300 ^[1] | 150 ^[2] |
| Crossed-over to Pomalidomide | 0 ^[3] | 11 ^[4] |
| Completed | 302 | 153 |

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Randomized subjects who received at least one dose of study drug (Completed indicates all subjects who had discontinued study drug).

[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: After Amendment 4 participants still on HD-Dex treatment were permitted to crossover to pomalidomide treatment

[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Not applicable to participants in this arm initially randomized to receive pomalidomide

[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: Only includes participants who discontinued treatment prior to disease progression who entered the PFS follow-up period.

Period 2

| | |
|------------------------------|---------------------|
| Period 2 title | PFS Follow-up Phase |
| Is this the baseline period? | No |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|--|
| Are arms mutually exclusive? | Yes |
| Arm title | Pomalidomide plus Low-Dose Dexamethasone |

Arm description:

Participants who received pomalidomide and low-dose dexamethasone during the treatment phase who discontinued treatment for reasons other than progressive disease were assessed for efficacy until disease progression during the PFS follow-up period.

| | |
|---|-----------------|
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

| | |
|--|-------------------------|
| Arm title | High-Dose Dexamethasone |
| Arm description: Participants who received high-dose dexamethasone during the treatment phase who discontinued treatment for reasons other than progressive disease were assessed for efficacy until disease progression during the PFS follow-up period. | |
| Arm type | No intervention |
| No investigational medicinal product assigned in this arm | |

| Number of subjects in period 2^[5] | Pomalidomide plus Low-Dose Dexamethasone | High-Dose Dexamethasone |
|---|--|-------------------------|
| Started | 11 | 8 |
| Completed | 11 | 8 |

Notes:

[5] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Randomized subjects who received at least one dose of study drug (Completed indicates all subjects who had discontinued study drug).

Baseline characteristics

Reporting groups

| | |
|--|--|
| Reporting group title | Pomalidomide plus Low-Dose Dexamethasone |
| Reporting group description: Participants received 4 mg pomalidomide administered by mouth on Days 1-21 of each 28-day treatment cycle and 40 mg dexamethasone (participants > 75 years of age received 20 mg dexamethasone) administered by mouth once per day on Days 1, 8, 15, and 22 of a 28-day cycle until disease progression. | |
| Reporting group title | High-Dose Dexamethasone |
| Reporting group description: Participants received 40 mg dexamethasone (participants > 75 years of age received 20 mg dexamethasone) administered by mouth once per day on Days 1 through 4, 9 through 12, and 17 through 20 of a 28-day cycle until disease progression. | |

| Reporting group values | Pomalidomide plus Low-Dose Dexamethasone | High-Dose Dexamethasone | Total |
|--|--|-------------------------|-------|
| Number of subjects | 302 | 153 | 455 |
| Age, Customized | | | |
| Stratification Factor 1 | | | |
| Units: Subjects | | | |
| ≤ 75 Years Old | 278 | 141 | 419 |
| > 75 Years Old | 24 | 12 | 36 |
| Age Continuous | | | |
| Units: years | | | |
| arithmetic mean | 63.6 | 63.7 | |
| standard deviation | ± 9.33 | ± 9.56 | - |
| Sex: Female, Male | | | |
| Units: Subjects | | | |
| Female | 121 | 66 | 187 |
| Male | 181 | 87 | 268 |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 27 | 14 | 41 |
| Not Hispanic or Latino | 228 | 104 | 332 |
| Unknown or Not Reported | 47 | 35 | 82 |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| Asian | 4 | 0 | 4 |
| Black or African American | 4 | 3 | 7 |
| White | 244 | 113 | 357 |
| Other | 2 | 2 | 4 |
| Not collected | 48 | 35 | 83 |
| Stratification Factor 2: Disease Population | | | |
| Disease Population Group 1 is defined as refractory patients who have progressed on or within 60 days of both lenalidomide and bortezomib based treatments. Disease Population Group 2 is defined as relapsed and refractory patients who achieved at least a partial response (PR) and progressed within 6 months after stopping treatment with lenalidomide and/or bortezomib. Disease Population Group 3 is defined as refractory/intolerant patients who developed intolerance/toxicity after a minimum of 2 cycles of bortezomib. | | | |
| Units: Subjects | | | |

| | | | |
|---|--------|--------|-----|
| Disease Population Group 1 | 249 | 125 | 374 |
| Disease Population Group 2 | 8 | 5 | 13 |
| Disease Population Group 3 | 45 | 23 | 68 |
| Stratification Factor 3: Number of Prior Anti-MM Therapies Units: Subjects | | | |
| 2 Prior Anti-MM Therapies | 17 | 8 | 25 |
| >2 Prior Anti-MM Therapies | 285 | 145 | 430 |
| Multiple Myeloma Stage before Study Entry | | | |
| The International Staging System divides myeloma into 3 stages based only on the serum beta-2 microglobulin and serum albumin levels. Stage I: Serum beta-2 microglobulin is less than 3.5 (mg/L) and the albumin level is above 3.5 (g/L); Stage II: Neither stage I or III, meaning that either: The beta-2 microglobulin level is between 3.5 and 5.5 (with any albumin level), OR The albumin is below 3.5 while the beta-2 microglobulin is less than 3.5 Stage III: Serum beta-2 microglobulin is greater than 5.5. | | | |
| Units: Subjects | | | |
| Stage I | 81 | 36 | 117 |
| Stage II | 115 | 56 | 171 |
| Stage III | 92 | 53 | 145 |
| Missing | 14 | 8 | 22 |
| Time from First Pathologic Diagnosis Units: years | | | |
| arithmetic mean | 6.2 | 6.5 | |
| standard deviation | ± 4.02 | ± 3.63 | - |

End points

End points reporting groups

| | |
|--|--|
| Reporting group title | Pomalidomide plus Low-Dose Dexamethasone |
| Reporting group description: Participants received 4 mg pomalidomide administered by mouth on Days 1-21 of each 28-day treatment cycle and 40 mg dexamethasone (participants > 75 years of age received 20 mg dexamethasone) administered by mouth once per day on Days 1, 8, 15, and 22 of a 28-day cycle until disease progression. | |
| Reporting group title | High-Dose Dexamethasone |
| Reporting group description: Participants received 40 mg dexamethasone (participants > 75 years of age received 20 mg dexamethasone) administered by mouth once per day on Days 1 through 4, 9 through 12, and 17 through 20 of a 28-day cycle until disease progression. | |
| Reporting group title | Pomalidomide plus Low-Dose Dexamethasone |
| Reporting group description: Participants who received pomalidomide and low-dose dexamethasone during the treatment phase who discontinued treatment for reasons other than progressive disease were assessed for efficacy until disease progression during the PFS follow-up period. | |
| Reporting group title | High-Dose Dexamethasone |
| Reporting group description: Participants who received high-dose dexamethasone during the treatment phase who discontinued treatment for reasons other than progressive disease were assessed for efficacy until disease progression during the PFS follow-up period. | |
| Subject analysis set title | HD-Dex / Pomalidomide |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Participants initially randomized to high-dose dexamethasone (HD-Dex) crossed over to receive 4 mg pomalidomide administered by mouth on Days 1-21 of each 28-day treatment cycle, with or without low-dose dexamethasone (40 mg for participants ≤ 75 years or 20 mg for participants > 75 years of age, administered orally once per day on Days 1, 8, 15, and 22 of each 28-day cycle) at the discretion of the investigator. Data include AEs that occurred after cross-over to pomalidomide. | |

Primary: Progression-free Survival (PFS) - Primary Analysis

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|---|--|
| End point title | Progression-free Survival (PFS) - Primary Analysis |
| End point description: Progression-free survival was calculated as the time from randomization to disease progression as determined by the Independent Response Adjudication Committee based on the International Myeloma Working Group Uniform Response criteria (IMWG), or death on study, whichever occurred earlier. Progressive disease required 1 of the following: • Increase of ≥ 25% from nadir in: o Serum M-component (absolute increase ≥ 0.5 g/dl); o Urine M-component (absolute increase ≥ 200 mg/24 hours); o Bone marrow plasma cell percentage (absolute % ≥ 10%); • Development of new or increase in the size of existing bone lesions or soft tissue plasmacytomas; • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dl) attributed solely to plasma cell proliferative disease. | |
| End point type | Primary |
| End point timeframe: From randomization until the data cut-off date of 07 September 2012. Maximum duration of follow-up for PFS assessments was 57 weeks. | |

| | | | | |
|----------------------------------|--|-------------------------|--|--|
| End point values | Pomalidomide plus Low-Dose Dexamethasone | High-Dose Dexamethasone | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 302 | 153 | | |
| Units: weeks | | | | |
| median (confidence interval 95%) | 15.7 (13.0 to 20.1) | 8.0 (7.0 to 9.0) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Analysis of Progression-free Survival |
| Comparison groups | Pomalidomide plus Low-Dose Dexamethasone v High-Dose Dexamethasone |
| Number of subjects included in analysis | 455 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[1] |
| Method | Stratified Log Rank Test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.45 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.35 |
| upper limit | 0.59 |

Notes:

[1] - Stratified by age, disease population, and prior number of anti myeloma therapy.

Primary: Progression-free Survival (PFS) with a Later Cut-off Date

| | |
|-----------------|---|
| End point title | Progression-free Survival (PFS) with a Later Cut-off Date |
|-----------------|---|

End point description:

Progression-free survival was calculated as the time from randomization to disease progression as determined by the Independent Response Adjudication Committee based on the International Myeloma Working Group Uniform Response criteria (IMWG), or death on study, whichever occurred earlier. Progressive disease requires 1 of the following: • Increase of $\geq 25\%$ from nadir in: o Serum M-component (absolute increase ≥ 0.5 g/dl); o Urine M-component (absolute increase ≥ 200 mg/24 hours); o Bone marrow plasma cell percentage (absolute % $\geq 10\%$); • Development of new or increase in the size of existing bone lesions or soft tissue plasmacytomas; • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dl) attributed solely to plasma cell proliferative disease.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

From randomization until the data cut-off date of 01 March 2013. Maximum duration of follow-up for PFS assessments was 74 weeks.

| | | | | |
|----------------------------------|--|-------------------------|--|--|
| End point values | Pomalidomide plus Low-Dose Dexamethasone | High-Dose Dexamethasone | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 302 | 153 | | |
| Units: weeks | | | | |
| median (confidence interval 95%) | 16.0 (13.0 to 19.6) | 8.1 (7.1 to 9.4) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Analysis of Progression-free Survival |
| Comparison groups | Pomalidomide plus Low-Dose Dexamethasone v High-Dose Dexamethasone |
| Number of subjects included in analysis | 455 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 ^[2] |
| Method | Stratified log-rank test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.49 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.39 |
| upper limit | 0.61 |

Notes:

[2] - Stratified by age, disease population, and prior number of anti myeloma therapy.

Secondary: Number of Participants with Adverse Events (AEs)

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

End point description:

An adverse event is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a participant during the course of a study. A serious AE is any AE occurring at any dose that: • Resulted in death; • Was life-threatening; • Required or prolonged existing inpatient hospitalization; • Resulted in persistent or significant disability/incapacity; • Was a congenital anomaly/birth defect; • Constitutes an important medical event. The Investigator assessed the relationship of each AE to study drug and graded the severity according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0): Grade 1 = Mild (no limitation in activity or intervention required); Grade 2 = Moderate (some limitation in activity; no/minimal medical intervention required); Grade 3 = Severe (marked limitation in activity; medical intervention required, hospitalization possible); Grade 4 = Life-threatening; Grade 5 = Death.

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

End point timeframe:

From first dose of study drug through to 30 days after the last dose as of the end of the study (29 August 2017); maximum time on treatment was 297, 269, and 239 weeks in the Pomalidomide + LD-Dex, HD-Dex, and cross-over groups respectively.

| End point values | Pomalidomide plus Low-Dose Dexamethasone | High-Dose Dexamethasone | HD-Dex / Pomalidomide | |
|---|--|-------------------------|-----------------------|--|
| Subject group type | Reporting group | Reporting group | Subject analysis set | |
| Number of subjects analysed | 300 ^[3] | 150 ^[4] | 11 | |
| Units: participants | | | | |
| Any adverse event | 298 | 149 | 11 | |
| Grade 3-4 adverse events | 266 | 127 | 8 | |
| AE related to pomalidomide | 251 | 0 | 11 | |
| AE related to dexamethasone | 205 | 115 | 5 | |
| AE related to either study drug | 271 | 115 | 11 | |
| Grade 3-4 AE related to pomalidomide | 199 | 0 | 6 | |
| Grade 3-4 AE related to dexamethasone | 114 | 70 | 2 | |
| Grade 3-4 AE related to either study drug | 212 | 70 | 6 | |
| Grade 5 adverse events | 46 | 21 | 1 | |
| Serious adverse events (SAEs) | 195 | 80 | 4 | |
| SAE related to pomalidomide | 89 | 0 | 1 | |
| SAE related to dexamethasone | 73 | 36 | 0 | |
| SAE related to either study drug | 98 | 36 | 1 | |
| SAE leading to discontinuation of pomalidomide | 20 | 0 | 1 | |
| SAE leading to discontinuation of dexamethasone | 20 | 14 | 1 | |
| SAE leading to discontinuation of either study drug | 23 | 14 | 1 | |
| AE leading to discontinuation of pomalidomide | 30 | 0 | 1 | |
| AE leading to discontinuation of dexamethasone | 34 | 16 | 1 | |
| AE leading to discontinuation of either study drug | 38 | 16 | 1 | |

Notes:

[3] - Randomized participants who received at least one dose of study drug

[4] - Randomized participants who received at least one dose of study drug

Statistical analyses

No statistical analyses for this end point

Secondary: Overall Survival - Primary Analysis

| | |
|-----------------|-------------------------------------|
| End point title | Overall Survival - Primary Analysis |
|-----------------|-------------------------------------|

End point description:

Overall survival is calculated as the time from randomization to death from any cause. Overall survival was censored at the last date that the participant was known to be alive for participants who were alive at the time of analysis and for participants who were lost to follow-up before death was documented.

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

End point timeframe:

From randomization until the data cut-off date of 07 September 2012. Maximum time on follow-up for survival was 70 weeks.

| End point values | Pomalidomide plus Low-Dose Dexamethasone | High-Dose Dexamethasone | | |
|----------------------------------|--|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 302 | 153 | | |
| Units: weeks | | | | |
| median (confidence interval 95%) | 99999 (48.1 to 99999) | 34.0 (23.4 to 39.9) | | |

Statistical analyses

| Statistical analysis title | Analysis of Overall Survival |
|---|--|
| Comparison groups | Pomalidomide plus Low-Dose Dexamethasone v High-Dose Dexamethasone |
| Number of subjects included in analysis | 455 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.53 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.37 |
| upper limit | 0.74 |

Secondary: Overall Survival with a Later Cut-off Date

| | |
|------------------------|---|
| End point title | Overall Survival with a Later Cut-off Date |
| End point description: | Overall survival is calculated as the time from randomization to death from any cause. Overall survival was censored at the last date that the participant was known to be alive for participants who were alive at the time of analysis and for participants who were lost to follow-up before death was documented. |
| End point type | Secondary |
| End point timeframe: | From randomization until the data cut-off date of 01 March 2013. Maximum time on follow-up for survival was 93 weeks. |

| End point values | Pomalidomide plus Low-Dose Dexamethasone | High-Dose Dexamethasone | | |
|----------------------------------|--|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 302 | 153 | | |
| Units: weeks | | | | |
| median (confidence interval 95%) | 54.0 (45.3 to | 34.9 (29.9 to | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Ananalysis of Overall Survival |
| Comparison groups | Pomalidomide plus Low-Dose Dexamethasone v High-Dose Dexamethasone |
| Number of subjects included in analysis | 455 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.009 |
| Method | Logrank |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.54 |
| upper limit | 0.92 |

Secondary: Overall Survival Based on the Final Dataset

| | |
|------------------------|---|
| End point title | Overall Survival Based on the Final Dataset |
| End point description: | Overall survival is calculated as the time from randomization to death from any cause. Overall survival was censored at the last date that the participant was known to be alive for participants who were alive at the time of analysis and for participants who were lost to follow-up before death was documented. |
| End point type | Secondary |
| End point timeframe: | From randomization until the data cut-off date of 29 August 2017. Maximum time on follow-up for survival was 324 weeks. |

| | | | | |
|----------------------------------|--|-------------------------|--|--|
| End point values | Pomalidomide plus Low-Dose Dexamethasone | High-Dose Dexamethasone | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 302 | 153 | | |
| Units: weeks | | | | |
| median (confidence interval 95%) | 56.1 (47.7 to 67.4) | 35.3 (29.9 to 39.9) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with an Objective Response According to International Myeloma Working Group (IMWG) Uniform Response Criteria

| | |
|-----------------|---|
| End point title | Percentage of Participants with an Objective Response According to International Myeloma Working Group (IMWG) Uniform Response Criteria |
|-----------------|---|

End point description:

Objective response is defined as a best overall response of stringent complete response (SCR), complete response (CR), very good partial response (VGPR) or partial response (PR) based on the Independent Response Adjudication Committee: SCR: CR and normal free light chain (FLC) ratio and no clonal cells in bone marrow; CR: Negative serum and urine on immunofixation, disappearance of any soft tissue plasmacytomas and $\leq 5\%$ plasma cells in bone marrow; VGPR: Serum and urine M-protein detectable by immunofixation but not on electrophoresis or $\geq 90\%$ reduction in serum M-protein and urine M-protein level < 100 mg/24 hours; PR: $\geq 50\%$ reduction of serum M-Protein and reduction in urinary M-protein by $\geq 90\%$ or to < 200 mg/24 hours. In addition to the above, if present at baseline a $\geq 50\%$ reduction in the size of soft tissue plasmacytomas is also required.

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

End point timeframe:

From randomization until the data cut-off date of 01 March 2013. Maximum time on follow-up was 93 weeks.

| End point values | Pomalidomide plus Low-Dose Dexamethasone | High-Dose Dexamethasone | | |
|-----------------------------------|--|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 302 | 153 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 23.5 | 3.9 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Analysis of Objective Response According to IMWG |
| Comparison groups | Pomalidomide plus Low-Dose Dexamethasone v High-Dose Dexamethasone |
| Number of subjects included in analysis | 455 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Fisher exact |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 7.53 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.19 |
| upper limit | 17.77 |

Secondary: Percentage of Participants with Objective Response According to European Group for Blood and Marrow Transplantation (EBMT) Criteria

| | |
|-----------------|---|
| End point title | Percentage of Participants with Objective Response According to European Group for Blood and Marrow Transplantation (EBMT) Criteria |
|-----------------|---|

End point description:

Objective response defined as a best overall response of complete response (CR) or partial response (PR) based on the Independent Response Adjudication Committee: CR requires all of the following: - Absence of original monoclonal paraprotein in serum and urine by immunofixation maintained at least 42 days. - <5% plasma cell in bone marrow aspirate and on bone marrow biopsy, if performed. - No increase in size or number of lytic bone lesions. - Disappearance of soft tissue plasmacytomas. PR requires all of the following: - $\geq 50\%$ reduction in level of serum monoclonal paraprotein, maintained at least 42 days. - Reduction in 24-hour urinary light chain extraction by $\geq 90\%$ or to < 200 mg, maintained at least 42 days. - For patients with non-secretory myeloma, $\geq 50\%$ reduction in plasma cells in bone marrow aspirate and on biopsy, if performed, for at least 42 days. - $\geq 50\%$ reduction in the size of soft tissue plasmacytomas. - No increase in size or number of lytic bone lesions.

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

End point timeframe:

From randomization until the data cut-off date of 01 March 2013. Maximum time on follow-up was 93 weeks.

| End point values | Pomalidomide plus Low-Dose Dexamethasone | High-Dose Dexamethasone | | |
|-----------------------------------|--|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 302 | 153 | | |
| Units: percentage of participants | | | | |
| number (not applicable) | 22.2 | 3.3 | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Analysis of Objective Response According to EBMT |
| Comparison groups | Pomalidomide plus Low-Dose Dexamethasone v High-Dose Dexamethasone |
| Number of subjects included in analysis | 455 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Fisher exact |
| Parameter estimate | Odds ratio (OR) |
| Point estimate | 8.44 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 3.32 |
| upper limit | 21.42 |

Secondary: Time to Progression

| | |
|-----------------|---------------------|
| End point title | Time to Progression |
|-----------------|---------------------|

End point description:

Time to progression (TTP) is calculated as the time from randomization to the first documented progression confirmed by a blinded, independent Response Adjudication Committee and based on the International Myeloma Working Group Uniform Response criteria (IMWG). Progressive disease requires 1 of the following: • Increase of $\geq 25\%$ from nadir in: o Serum M-component (absolute increase ≥ 0.5 g/dl); o Urine M-component (absolute increase ≥ 200 mg/24 hours); o Bone marrow plasma cell percentage (absolute % $\geq 10\%$); • Development of new or increase in the size of existing bone lesions or soft tissue plasmacytomas; • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dl) attributed solely to plasma cell proliferative disease.

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

End point timeframe:

From randomization until the data cut-off date of 01 March 2013. Maximum time on follow-up was 93 weeks.

| End point values | Pomalidomide plus Low-Dose Dexamethasone | High-Dose Dexamethasone | | |
|----------------------------------|--|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 302 | 153 | | |
| Units: weeks | | | | |
| median (confidence interval 95%) | 20.0 (16.1 to 24.0) | 9.0 (8.0 to 10.9) | | |

Statistical analyses

| | |
|---|--|
| Statistical analysis title | Analysis of Time to Progression |
| Comparison groups | High-Dose Dexamethasone v Pomalidomide plus Low-Dose Dexamethasone |
| Number of subjects included in analysis | 455 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 [5] |
| Method | Stratified Log Rank Test |
| Parameter estimate | Hazard ratio (HR) |
| Point estimate | 0.46 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.36 |
| upper limit | 0.59 |

Notes:

[5] - Stratified by age, diseases population, and prior number of anti myeloma therapy.

Secondary: Time to Response

| | |
|-----------------|------------------|
| End point title | Time to Response |
|-----------------|------------------|

End point description:

Time to response is calculated as the time from randomization to the initial documented response (partial response or better) based on IMWG criteria. SCR: CR and normal free light chain (FLC) ratio and no clonal cells in bone marrow; CR: Negative serum and urine on immunofixation, disappearance of any soft tissue plasmacytomas and $\leq 5\%$ plasma cells in bone marrow; VGPR: Serum and urine M-protein detectable by immunofixation but not on electrophoresis or $\geq 90\%$ reduction in serum M-protein and urine M-protein level < 100 mg/24 hours; PR: $\geq 50\%$ reduction of serum M-Protein and reduction in urinary M-protein by $\geq 90\%$ or to < 200 mg/24 hours. If present at baseline a $\geq 50\%$ reduction in size of soft tissue plasmacytomas is also required.

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

End point timeframe:

From randomization until the data cut-off date of 01 March 2013. Maximum time on follow-up was 93 weeks.

| End point values | Pomalidomide plus Low-Dose Dexamethasone | High-Dose Dexamethasone | | |
|-------------------------------|--|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 71 ^[6] | 6 ^[7] | | |
| Units: weeks | | | | |
| median (full range (min-max)) | 8.1 (4.0 to 48.0) | 10.5 (4.1 to 42.1) | | |

Notes:

[6] - Randomized participants with a response

[7] - Randomized participants with a response

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of Response

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

End point description:

Duration of response (calculated for responders only) is defined as time from the initial documented response (partial response or better) to confirmed disease progression, based on IMWG criteria assessed by the Independent Response Adjudication Committee.

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

End point timeframe:

From randomization until the data cut-off date of 01 March 2013. Maximum time on follow-up was 93 weeks.

| End point values | Pomalidomide plus Low-Dose Dexamethasone | High-Dose Dexamethasone | | |
|----------------------------------|--|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 71 ^[8] | 6 ^[9] | | |
| Units: weeks | | | | |
| median (confidence interval 95%) | 35.1 (28.4 to 52.9) | 28.1 (20.1 to 37.1) | | |

Notes:

[8] - Randomized participants with a response

[9] - Randomized participants with a response

Statistical analyses

No statistical analyses for this end point

Secondary: Time to the First Hemoglobin Improvement

| | |
|-----------------|--|
| End point title | Time to the First Hemoglobin Improvement |
|-----------------|--|

End point description:

Time to increased hemoglobin, defined as the time from randomization to at least one category improvement from Baseline in common terminology criteria for adverse events (CTCAE) grade for hemoglobin level. Hemoglobin categories are: 1) Normal; 2) CTCAE Grade 1: < lower limit of normal (LLN) to 10.0 g/dL; 3) CTCAE Grade 2: < 10.0 to <8.0 g/dL. Participants with CTCAE Grade 3 anemia or worse at Baseline were excluded from the study.

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

End point timeframe:

From randomization until the data cut-off date of 01 March 2013. Maximum time on follow-up was 93 weeks.

| End point values | Pomalidomide plus Low-Dose Dexamethasone | High-Dose Dexamethasone | | |
|-------------------------------|--|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 144 ^[10] | 50 ^[11] | | |
| Units: weeks | | | | |
| median (full range (min-max)) | 3.4 (1.1 to 49.3) | 1.3 (0.9 to 24.3) | | |

Notes:

[10] - Randomized participants with improvement in hemoglobin during the study

[11] - Randomized participants with improvement in hemoglobin during the study

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Improvement in Bone Pain

| | |
|-----------------|----------------------------------|
| End point title | Time to Improvement in Bone Pain |
|-----------------|----------------------------------|

End point description:

Time to improvement in bone pain is defined as the time from randomization to at least one category improvement from Baseline in bone pain category. Bone pain was categorized (from best to worst) according to answers to the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire for patients with Multiple Myeloma Module (QLQ-MY20), Question 1, "Have

you had bone aches or pain?": 1) Not at all, 2) A little, 3) Quite a bit, or 4) Very much.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From randomization until the data cut-off date of 01 March 2013. Maximum time on follow-up was 93 weeks. | |

| End point values | Pomalidomide plus Low-Dose Dexamethasone | High-Dose Dexamethasone | | |
|-------------------------------|--|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 101 ^[12] | 37 ^[13] | | |
| Units: weeks | | | | |
| median (full range (min-max)) | 5.7 (3.7 to 88.6) | 4.1 (3.7 to 27.3) | | |

Notes:

[12] - Randomized participants with improvement in bone pain

[13] - Randomized participants with improvement in bone pain

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Improvement in Renal Function

| | |
|--|---------------------------------------|
| End point title | Time to Improvement in Renal Function |
| End point description: | |
| Time to improvement in renal function is defined as the time from randomization to at least one category improvement from Baseline in renal function. Renal Function was categorized as (from best to worst): • Normal: creatinine clearance ≥ 80 mL/min; • Grade 1: creatinine clearance ≥ 60 to < 80 mL/min; • Grade 2 : creatinine clearance ≥ 45 to < 60 mL/min. Participants with creatinine clearance < 45 mL/min at baseline were excluded from the study. | |
| End point type | Secondary |
| End point timeframe: | |
| From randomization until the data cut-off date of 01 March 2013. Maximum time on follow-up was 93 weeks. | |

| End point values | Pomalidomide plus Low-Dose Dexamethasone | High-Dose Dexamethasone | | |
|-------------------------------|--|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 94 ^[14] | 45 ^[15] | | |
| Units: weeks | | | | |
| median (full range (min-max)) | 4.6 (3.3 to 45.6) | 4.1 (3.3 to 28.1) | | |

Notes:

[14] - Randomized participants with improvement in renal function

[15] - Randomized participants with improvement in renal function

Statistical analyses

Secondary: Time to Improvement in Eastern Cooperative Oncology Group (ECOG) Performance Status

| | |
|-----------------|---|
| End point title | Time to Improvement in Eastern Cooperative Oncology Group (ECOG) Performance Status |
|-----------------|---|

End point description:

Time to improvement in ECOG performance status defined as the time from randomization until at least a one category improvement from Baseline in ECOG performance status score. The categories of the ECOG Performance Status Scale are as follows: -0: Fully active, able to carry on all pre-disease performance without restriction; -1: Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work; -2: Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours. Patients with a score of 3, 4 or 5 were excluded from participating in the study.

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

End point timeframe:

From randomization until the data cut-off date of 01 March 2013. Maximum time on follow-up was 93 weeks.

| End point values | Pomalidomide plus Low-Dose Dexamethasone | High-Dose Dexamethasone | | |
|-------------------------------|--|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 61 ^[16] | 18 ^[17] | | |
| Units: weeks | | | | |
| median (full range (min-max)) | 8.1 (4.1 to 44.1) | 4.3 (4.1 to 33.7) | | |

Notes:

[16] - Randomized participants with improvement in ECOG performance status during the study

[17] - Randomized participants with improvement in ECOG performance status during the study

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the European Organization for Research and Treatment of Cancer Cancer Quality of Life Questionnaire for Patients with Cancer (EORTC QLQ-C30) Global Health Status Domain

| | |
|-----------------|--|
| End point title | Change from Baseline in the European Organization for Research and Treatment of Cancer Cancer Quality of Life Questionnaire for Patients with Cancer (EORTC QLQ-C30) Global Health Status Domain |
|-----------------|--|

End point description:

The European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life (QOL) questionnaire (EORTC QLQ-C30) is a 30-question tool used to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Global Health Status/QOL scale is scored between 0 and 100, with a high score indicating better Global Health Status/QOL. Negative change from Baseline values indicate deterioration in QOL or functioning and positive values indicate improvement. The Patient Reported Outcomes (PRO) population includes randomized participants with 1 active treatment and 1 PRO measurement item completed. Only participants with available data at Baseline and each time point are included.

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

End point timeframe:

Day 1 of Cycle 1 (Baseline), and Day 1 of Cycles 2, 3, 4, 5 and 6

| End point values | Pomalidomide plus Low-Dose Dexamethasone | High-Dose Dexamethasone | | |
|--------------------------------------|--|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 289 ^[18] | 144 ^[19] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 2, Day 1 (N=209, 91) | 0.52 (± 23.01) | -3.75 (± 24.10) | | |
| Cycle 3, Day 1 (N=175, 53) | 2.67 (± 24.97) | -2.36 (± 21.08) | | |
| Cycle 4, Day 1 (N=157, 33) | 0.80 (± 24.62) | -3.03 (± 22.42) | | |
| Cycle 5 Day 1 (N=130, 27) | 0.51 (± 26.81) | 0.00 (± 27.44) | | |
| Cycle 6, Day 1 (N=116, 18) | -2.51 (± 25.57) | -0.93 (± 17.59) | | |

Notes:

[18] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed

[19] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the EORTC QLQ-C30 Physical functioning Domain

| | |
|-----------------|---|
| End point title | Change from Baseline in the EORTC QLQ-C30 Physical functioning Domain |
|-----------------|---|

End point description:

The European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life (QOL) questionnaire (EORTC QLQ-C30) is a 30-question tool used in clinical research to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Physical Functioning Scale is scored between 0 and 100, with a high score indicating better functioning/support. Negative change from Baseline values indicate deterioration in functioning and positive values indicate improvement.

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

End point timeframe:

Day 1 of Cycle 1 (Baseline), and Day 1 of Cycles 2, 3, 4, 5 and 6

| End point values | Pomalidomide plus Low-Dose Dexamethasone | High-Dose Dexamethasone | | |
|--------------------------------------|--|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 289 ^[20] | 144 ^[21] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 2, Day 1 (N=210, 91) | -2.32 (± 18.25) | -3.96 (± 18.35) | | |
| Cycle 3, Day 1 (N=177, 53) | -0.56 (± 19.86) | -9.69 (± 16.67) | | |
| Cycle 4, Day 1 (N=159, 33) | 0.17 (± 20.25) | -8.08 (± 13.31) | | |
| Cycle 5 Day 1 (N=132, 27) | 0.91 (± 19.92) | -5.43 (± 19.31) | | |
| Cycle 6, Day 1 (N=118, 18) | 0.54 (± 21.30) | -4.81 (± 14.24) | | |

Notes:

[20] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed

[21] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the EORTC QLQ-C30 Emotional functioning Domain

| | |
|-----------------|--|
| End point title | Change from Baseline in the EORTC QLQ-C30 Emotional functioning Domain |
|-----------------|--|

End point description:

The European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life (QOL) questionnaire (EORTC QLQ-C30) is a 30-question tool used in clinical research to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Emotional Functioning Scale is scored between 0 and 100, with a high score indicating better functioning/support. Negative change from Baseline values indicate deterioration in functioning and positive values indicate improvement.

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

End point timeframe:

Day 1 of Cycle 1 (Baseline), and Day 1 of Cycles 2, 3, 4, 5 and 6

| End point values | Pomalidomide plus Low-Dose Dexamethasone | High-Dose Dexamethasone | | |
|--------------------------------------|--|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 289 ^[22] | 144 ^[23] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 2, Day 1 (N=210, 91) | 1.22 (± 21.44) | -2.87 (± 21.57) | | |

| | | | | |
|----------------------------|----------------|-----------------|--|--|
| Cycle 3, Day 1 (N=176, 53) | 2.40 (± 20.36) | -5.66 (± 25.36) | | |
| Cycle 4, Day 1 (N=158, 33) | 2.44 (± 21.05) | -6.31 (± 23.48) | | |
| Cycle 5 Day 1 (N=131, 27) | 1.91 (± 21.97) | -8.64 (± 23.17) | | |
| Cycle 6, Day 1 (N=117, 18) | 0.19 (± 22.30) | -4.17 (± 13.18) | | |

Notes:

[22] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed

[23] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the EORTC QLQ-C30 Fatigue Domain

| | |
|-----------------|--|
| End point title | Change from Baseline in the EORTC QLQ-C30 Fatigue Domain |
|-----------------|--|

End point description:

The European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life (QOL) questionnaire (EORTC QLQ-C30) is a 30-question tool used in clinical research to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Fatigue Scale is scored between 0 and 100, with a high score indicating a higher level of symptoms. Negative change from Baseline values indicate reduction in fatigue (i.e. improvement in symptom) and positive values indicate increases in fatigue (i.e. worsening of symptom).

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

End point timeframe:

Day 1 of Cycle 1 (Baseline), and Day 1 of Cycles 2, 3, 4, 5 and 6

| End point values | Pomalidomide plus Low-Dose Dexamethasone | High-Dose Dexamethasone | | |
|--------------------------------------|--|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 289 ^[24] | 144 ^[25] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 2, Day 1 (N=210, 91) | 2.43 (± 27.39) | 4.03 (± 25.37) | | |
| Cycle 3, Day 1 (N=177, 53) | 3.26 (± 27.66) | 7.76 (± 23.73) | | |
| Cycle 4, Day 1 (N=159, 33) | 1.71 (± 26.21) | 9.43 (± 28.88) | | |
| Cycle 5 Day 1 (N=132, 27) | 0.21 (± 28.41) | 9.47 (± 23.00) | | |
| Cycle 6, Day 1 (N=118, 18) | 0.99 (± 31.13) | 10.49 (± 16.38) | | |

Notes:

[24] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed

[25] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the EORTC QLQ-C30 Pain Domain

| | |
|-----------------|---|
| End point title | Change from Baseline in the EORTC QLQ-C30 Pain Domain |
|-----------------|---|

End point description:

The European Organization for Research and Treatment of Cancer (EORTC) Core Quality of Life (QOL) questionnaire (EORTC QLQ-C30) is a 30-question tool used in clinical research to assess the overall quality of life in cancer patients. It consists of 15 domains: 1 global health status (GHS) scale, 5 functional scales (Physical, Role, Cognitive, Emotional, Social), and 9 symptom scales/items (Fatigue, Nausea and Vomiting, Pain, Dyspnea, Sleep Disturbance, Appetite Loss, Constipation, Diarrhea, Financial Impact). The EORTC QLQ-C30 Pain Scale is scored between 0 and 100, with a high score indicating a higher level of symptoms. Negative change from Baseline values indicate reductions in pain (i.e. improvement in symptom) and positive values indicate increases in pain (i.e. worsening of symptom).

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

End point timeframe:

Day 1 of Cycle 1 (Baseline), and Day 1 of Cycles 2, 3, 4, 5 and 6

| End point values | Pomalidomide plus Low-Dose Dexamethasone | High-Dose Dexamethasone | | |
|--------------------------------------|--|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 289 ^[26] | 144 ^[27] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 2, Day 1 (N=210, 92) | -2.70 (± 25.74) | 0.36 (± 25.32) | | |
| Cycle 3, Day 1 (N=177, 53) | -3.58 (± 29.62) | 2.83 (± 25.47) | | |
| Cycle 4, Day 1 (N=159, 33) | -2.41 (± 30.52) | 3.03 (± 25.84) | | |
| Cycle 5 Day 1 (N=132, 27) | -1.64 (± 28.00) | 2.47 (± 31.59) | | |
| Cycle 6, Day 1 (N=118, 18) | -2.40 (± 30.99) | 10.19 (± 23.67) | | |

Notes:

[26] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed

[27] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the European Organization for Research and Treatment of Cancer QoL Questionnaire for Patients with Multiple Myeloma (EORTC QLQ-MY20) Disease Symptoms

| | |
|-----------------|---|
| End point title | Change from Baseline in the European Organization for Research and Treatment of Cancer QoL Questionnaire for Patients with Multiple Myeloma (EORTC QLQ-MY20) Disease Symptoms |
|-----------------|---|

End point description:

The European Organization for Research and Treatment of Cancer QoL Questionnaire for Patients with Multiple Myeloma (EORTC QLQ-MY20) is a 20-question tool used in clinical research to assess health-

related quality of life in multiple myeloma patients. The QLQ-MY20 includes four domains (Disease Symptoms, Side-Effects of Treatment, Body Image and Future Perspective). The EORTC QLQ-MY20 Disease Symptoms Scale is scored between 0 and 100, with a high score reflecting a higher level of symptoms. Negative change from Baseline values indicate reduction (i.e. improvement) in symptoms and positive values indicate increase (i.e. worsening) of symptoms.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Day 1 of Cycle 1 (Baseline), and Day 1 of Cycles 2, 3, 4, 5 and 6 | |

| End point values | Pomalidomide plus Low-Dose Dexamethasone | High-Dose Dexamethasone | | |
|--------------------------------------|--|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 289 ^[28] | 144 ^[29] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 2, Day 1 (N=218, 99) | -0.50 (± 16.51) | -1.07 (± 17.78) | | |
| Cycle 3, Day 1 (N=180, 56) | -1.36 (± 19.51) | 0.97 (± 19.93) | | |
| Cycle 4, Day 1 (N=161, 37) | -1.15 (± 19.54) | 1.35 (± 16.94) | | |
| Cycle 5 Day 1 (N=135, 30) | -0.53 (± 17.39) | 1.48 (± 17.56) | | |
| Cycle 6, Day 1 (N=115, 21) | 0.60 (± 19.64) | 2.12 (± 13.43) | | |

Notes:

[28] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed

[29] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the EORTC QLQ-MY20 Side Effects Domain

| | |
|-----------------|--|
| End point title | Change from Baseline in the EORTC QLQ-MY20 Side Effects Domain |
|-----------------|--|

End point description:

The European Organization for Research and Treatment of Cancer QoL Questionnaire for Patients with Multiple Myeloma (EORTC QLQ-MY20) is a 20-question tool used in clinical research to assess health-related quality of life in multiple myeloma patients. The QLQ-MY20 includes four domains (Disease Symptoms, Side-Effects of Treatment, Body Image and Future Perspective). The EORTC QLQ-MY20 Side Effects Scale is scored between 0 and 100, with a high score reflecting a higher level of symptoms. Negative change from Baseline values indicate reduction in side effects (i.e. improvement in symptom) and positive values indicate increase in side effects (i.e. worsening of symptom).

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Day 1 of Cycle 1 (Baseline), and Day 1 of Cycles 2, 3, 4, 5 and 6 | |

| End point values | Pomalidomide plus Low-Dose Dexamethasone | High-Dose Dexamethasone | | |
|--------------------------------------|--|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 289 ^[30] | 144 ^[31] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 2, Day 1 (N=218, 99) | 2.71 (± 13.90) | 2.61 (± 13.34) | | |
| Cycle 3, Day 1 (N=180, 55) | 3.26 (± 13.72) | 5.35 (± 12.27) | | |
| Cycle 4, Day 1 (N=161, 37) | 3.73 (± 14.47) | 7.46 (± 11.61) | | |
| Cycle 5 Day 1 (N=135, 30) | 4.74 (± 14.45) | 6.89 (± 10.32) | | |
| Cycle 6, Day 1 (N=115, 21) | 4.55 (± 15.76) | 7.30 (± 9.35) | | |

Notes:

[30] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed

[31] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the European Quality of Life-5 Dimensions (EQ-5D) Utility Index Score

| | |
|-----------------|---|
| End point title | Change from baseline in the European Quality of Life-5 Dimensions (EQ-5D) Utility Index Score |
|-----------------|---|

End point description:

EQ-5D is a self-administered questionnaire that assesses health-related quality of life (QOL). The EQ-5D descriptive health profile comprises five dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension has 3 levels of response: No problem (1), some problems (2), and extreme problems (3). A unique EQ-5D health state is defined by combining one level from each of the five dimensions into a single utility index score. EQ-5D index values range from -0.59 to 1.00 where an EQ-5D score of 1.00 equals "perfect health", a score of 0 equals "death" and a score of -0.59 equals worst imaginable health state. A positive change from Baseline score indicates improvement in health status. A negative change from Baseline score indicates worsening in health status. Negative scores represent the possible though unlikely situation that a patient's QOL is worse than death, i.e. they would rather be dead than living with that QOL

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

End point timeframe:

Day 1 of Cycle 1 (Baseline), and Day 1 of Cycles 2, 3, 4, 5 and 6

| End point values | Pomalidomide plus Low-Dose Dexamethasone | High-Dose Dexamethasone | | |
|--------------------------------------|--|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 289 ^[32] | 144 ^[33] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cycle 2, Day 1 (N=198, 89) | -0.03 (± 0.28) | -0.02 (± 0.23) | | |
| Cycle 3, Day 1 (N=167, 52) | 0.01 (± 0.29) | -0.06 (± 0.27) | | |
| Cycle 4, Day 1 (N=146, 33) | 0.04 (± 0.31) | -0.07 (± 0.29) | | |
| Cycle 5, Day 1 (N=125, 25) | 0.01 (± 0.32) | -0.04 (± 0.26) | | |
| Cycle 6, Day 1 (N=108, 18) | 0.03 (± 0.31) | -0.12 (± 0.19) | | |

Notes:

[32] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed

[33] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed

Statistical analyses

No statistical analyses for this end point

Secondary: Time to First Worsening of Quality of Life (QOL) Domains

| | |
|-----------------|--|
| End point title | Time to First Worsening of Quality of Life (QOL) Domains |
|-----------------|--|

End point description:

Time to worsening in quality of life domains was calculated as the time from Baseline to the first worsened minimally important difference (MID), defined as the smallest change in a QOL score considered important to patients that would lead the patient or clinician to consider a change in therapy. MID thresholds were calculated in Standard Error of Measurement (SEM) units using the Baseline QOL data. Based on the MID, participants were classified as worsened according to the following: For the EORTC QLQ-C30 global health status and functional scales and the EQ-5D health utility score, participants were classified as worsened if their change from Baseline score was less than -1 SEM. For the EORTC QLQ-C30 symptom scores (fatigue and pain) and EORTC QLQ-MY20 disease symptoms and side effects scales, participants were classified as worsened if their change from Baseline score was greater than 1 SEM. See previous outcome measures for definitions of each scale.

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

End point timeframe:

Assessed on Day 1 of the first 6 treatment cycles.

| End point values | Pomalidomide plus Low-Dose Dexamethasone | High-Dose Dexamethasone | | |
|----------------------------------|--|-------------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 289 ^[34] | 144 ^[35] | | |
| Units: days | | | | |
| median (confidence interval 95%) | | | | |
| Global Health Status | 71 (60 to 92) | 57 (36 to 91) | | |
| Physical Functioning | 128 (92 to 225) | 67 (57 to 106) | | |
| Emotional Functioning | 146 (120 to 259) | 85 (57 to 124) | | |
| Fatigue | 58 (57 to 85) | 57 (46 to 67) | | |
| Pain | 92 (86 to 147) | 85 (62 to 337) | | |
| Disease Symptoms | 127 (92 to 155) | 106 (67 to 141) | | |
| Side Effects of Treatment | 90 (78 to 123) | 85 (58 to 113) | | |
| Health Utility | 225 (123 to 338) | 162 (85 to 99999) | | |

Notes:

[34] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed

[35] - Randomized participants with ≥ 1 active treatment and at least 1 PRO measurement item completed

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug through to 30 days after the last dose as of the end of the study (29 August 2017); maximum time on treatment was 297, 269, and 239 weeks in the Pomalidomide + LD-Dex, HD-Dex, and cross-over groups respectively.

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

Dictionary used

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

| | |
|--------------------|----|
| Dictionary version | 19 |
|--------------------|----|

Reporting groups

| | |
|-----------------------|--|
| Reporting group title | Pomalidomide Plus Low-Dose Dexamethasone |
|-----------------------|--|

Reporting group description:

Participants received 4 mg pomalidomide administered by mouth on Days 1-21 of each 28-day treatment cycle and 40 mg dexamethasone (participants > 75 years of age received 20 mg dexamethasone) administered by mouth once per day on Days 1, 8, 15, and 22 of a 28-day cycle until disease progression.

| | |
|-----------------------|--|
| Reporting group title | High-Dose Dexamethasone (BEFORE CROSSOVER) |
|-----------------------|--|

Reporting group description:

Participants received 40 mg dexamethasone (participants > 75 years of age received 20 mg dexamethasone) administered by mouth once per day on Days 1 through 4, 9 through 12, and 17 through 20 of a 28-day cycle until disease progression, or until cross-over to pomalidomide. Data are up to the time of cross-over.

| | |
|-----------------------|--|
| Reporting group title | High Dose Dexamethasone/Pomalidomide (AFTER CROSSOVER) |
|-----------------------|--|

Reporting group description:

Participants initially randomized to high-dose dexamethasone (HD-Dex) crossed over to receive 4 mg pomalidomide administered by mouth on Days 1-21 of each 28-day treatment cycle, with or without low-dose dexamethasone (40 mg for participants ≤ 75 years or 20 mg for participants > 75 years of age, administered orally once per day on Days 1, 8, 15, and 22 of each 28-day cycle) at the discretion of the investigator. Data include AEs that occurred after cross-over to pomalidomide.

| Serious adverse events | Pomalidomide Plus Low-Dose Dexamethasone | High-Dose Dexamethasone (BEFORE CROSSOVER) | High Dose Dexamethasone/Pomalidomide (AFTER CROSSOVER) |
|---|--|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 195 / 300 (65.00%) | 80 / 150 (53.33%) | 4 / 11 (36.36%) |
| number of deaths (all causes) | 252 | 124 | 8 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Basal cell carcinoma | | | |
| subjects affected / exposed | 3 / 300 (1.00%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 2 / 8 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Plasma cell leukaemia | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 300 (0.33%) | 2 / 150 (1.33%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Plasma cell myeloma | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Plasmacytoma | | | |
| subjects affected / exposed | 3 / 300 (1.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate cancer stage IV | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Squamous cell carcinoma of skin | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tumour pain | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vascular disorders | | | |
| Axillary vein thrombosis | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Circulatory collapse | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Deep vein thrombosis | | | |

| | | | |
|--|-----------------|-----------------|----------------|
| subjects affected / exposed | 2 / 300 (0.67%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertension | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertensive crisis | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypotension | | | |
| subjects affected / exposed | 2 / 300 (0.67%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General disorders and administration site conditions | | | |
| Adverse drug reaction | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Asthenia | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 2 / 150 (1.33%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Catheter site haemorrhage | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Fatigue | | | |
| subjects affected / exposed | 3 / 300 (1.00%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| General physical health deterioration | | | |

| | | | |
|---|------------------|------------------|----------------|
| subjects affected / exposed | 26 / 300 (8.67%) | 12 / 150 (8.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 2 / 34 | 1 / 18 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 17 | 0 / 6 | 0 / 0 |
| Hyperthermia | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Malaise | | | |
| subjects affected / exposed | 2 / 300 (0.67%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Multiple organ dysfunction syndrome | | | |
| subjects affected / exposed | 4 / 300 (1.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| Non-cardiac chest pain | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oedema peripheral | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain | | | |
| subjects affected / exposed | 2 / 300 (0.67%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Performance status decreased | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pyrexia | | | |

| | | | |
|---|------------------|-----------------|----------------|
| subjects affected / exposed | 26 / 300 (8.67%) | 7 / 150 (4.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 15 / 35 | 4 / 9 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sudden death | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Acute pulmonary oedema | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atelectasis | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Chronic obstructive pulmonary disease | | | |
| subjects affected / exposed | 2 / 300 (0.67%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Cough | | | |
| subjects affected / exposed | 2 / 300 (0.67%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspnoea | | | |
| subjects affected / exposed | 9 / 300 (3.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 5 / 11 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epistaxis | | | |
| subjects affected / exposed | 3 / 300 (1.00%) | 2 / 150 (1.33%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung disorder | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 2 / 300 (0.67%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lung infiltration | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonitis | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Productive cough | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |
| subjects affected / exposed | 5 / 300 (1.67%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 4 / 5 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary oedema | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 2 / 150 (1.33%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory failure | | | |
| subjects affected / exposed | 3 / 300 (1.00%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Aggression | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bradyphrenia | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Confusional state | | | |
| subjects affected / exposed | 3 / 300 (1.00%) | 3 / 150 (2.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 2 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Delirium | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Investigations | | | |
| Blood creatinine increased | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 2 / 150 (1.33%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood immunoglobulin M increased | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| C-reactive protein increased | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Platelet count decreased | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| Femoral neck fracture | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Femur fracture | | | |
| subjects affected / exposed | 5 / 300 (1.67%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 5 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hip fracture | | | |
| subjects affected / exposed | 2 / 300 (0.67%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Humerus fracture | | | |
| subjects affected / exposed | 2 / 300 (0.67%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lumbar vertebral fracture | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Overdose | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pelvic fracture | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Post procedural haematoma | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rib fracture | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 300 (0.33%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal compression fracture | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural haematoma | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Angina pectoris | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial fibrillation | | | |
| subjects affected / exposed | 7 / 300 (2.33%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 3 / 12 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial tachycardia | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac amyloidosis | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Cardiac arrest | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 300 (0.33%) | 1 / 150 (0.67%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 1 |
| Cardiac failure | | | |
| subjects affected / exposed | 4 / 300 (1.33%) | 2 / 150 (1.33%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 2 / 6 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure acute | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac failure congestive | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardio-respiratory arrest | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Ischaemic cardiomyopathy | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 2 / 300 (0.67%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial ischaemia | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus bradycardia | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinus node dysfunction | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tachycardia | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ventricular tachycardia | | | |
| subjects affected / exposed | 2 / 300 (0.67%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Cerebrovascular accident | | | |
| subjects affected / exposed | 2 / 300 (0.67%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cognitive disorder | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Coma | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Depressed level of consciousness | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 2 / 300 (0.67%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dizziness | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dyspraxia | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Encephalopathy | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epilepsy | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hemiparesis | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic cerebral infarction | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Loss of consciousness | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neurological decompensation | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Parkinson's disease | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Partial seizures | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Post herpetic neuralgia | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Presyncope | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Radiculopathy | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Seizure | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal cord compression | | | |

| | | | |
|---|------------------|-----------------|----------------|
| subjects affected / exposed | 2 / 300 (0.67%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subarachnoid haemorrhage | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 2 / 300 (0.67%) | 0 / 150 (0.00%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Transient ischaemic attack | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vertigo CNS origin | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 10 / 300 (3.33%) | 7 / 150 (4.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 6 / 11 | 0 / 7 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood disorder | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Febrile neutropenia | | | |
| subjects affected / exposed | 19 / 300 (6.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 34 / 40 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhagic anaemia | | | |

| | | | |
|---|------------------|-----------------|----------------|
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperviscosity syndrome | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 2 / 150 (1.33%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |
| subjects affected / exposed | 10 / 300 (3.33%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 9 / 10 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancytopenia | | | |
| subjects affected / exposed | 2 / 300 (0.67%) | 2 / 150 (1.33%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 6 / 300 (2.00%) | 4 / 150 (2.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 3 / 6 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ear and labyrinth disorders | | | |
| Otorrhoea | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Blepharitis | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diplopia | | | |
| subjects affected / exposed | 2 / 300 (0.67%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 300 (0.67%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Constipation | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dental caries | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |
| subjects affected / exposed | 2 / 300 (0.67%) | 2 / 150 (1.33%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enteritis | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Haemorrhoids | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Incarcerated inguinal hernia | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Large intestine perforation | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Melaena | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Necrotising colitis | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Oesophagitis | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Papilla of Vater stenosis | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Retroperitoneal haemorrhage | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Stomatitis | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 2 / 300 (0.67%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholestasis | | | |

| | | | |
|---|------------------|-----------------|----------------|
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gallbladder perforation | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatic mass | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin and subcutaneous tissue disorders | | | |
| Acute febrile neutrophilic dermatosis | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal and urinary disorders | | | |
| Acute kidney injury | | | |
| subjects affected / exposed | 11 / 300 (3.67%) | 7 / 150 (4.67%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 1 / 19 | 0 / 7 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| Crush syndrome | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure | | | |
| subjects affected / exposed | 8 / 300 (2.67%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 3 / 8 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal impairment | | | |
| subjects affected / exposed | 4 / 300 (1.33%) | 2 / 150 (1.33%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary retention | | | |

| | | | |
|---|------------------|-----------------|----------------|
| subjects affected / exposed | 3 / 300 (1.00%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthritis reactive | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Back pain | | | |
| subjects affected / exposed | 8 / 300 (2.67%) | 2 / 150 (1.33%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 9 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bone pain | | | |
| subjects affected / exposed | 10 / 300 (3.33%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 10 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Groin pain | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral disc compression | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Joint swelling | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Muscular weakness | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 2 / 150 (1.33%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal chest pain | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myalgia | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myopathy | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neck pain | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteonecrosis of jaw | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 2 / 300 (0.67%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain in jaw | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pathological fracture | | | |
| subjects affected / exposed | 2 / 300 (0.67%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal pain | | | |
| subjects affected / exposed | 2 / 300 (0.67%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Abscess limb | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Acute sinusitis | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Anal abscess | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Aspergillus infection | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacteraemia | | | |
| subjects affected / exposed | 2 / 300 (0.67%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacterial diarrhoea | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacterial infection | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bacterial sepsis | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchitis | | | |
| subjects affected / exposed | 8 / 300 (2.67%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 2 / 8 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Bronchopulmonary aspergillosis | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 2 / 300 (0.67%) | 0 / 150 (0.00%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Conjunctivitis | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cytomegalovirus chorioretinitis | | | |
| subjects affected / exposed | 2 / 300 (0.67%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device related infection | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 3 / 300 (1.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Device related sepsis | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diverticulitis | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterobacter infection | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Enterobacter sepsis | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Erysipelas | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia infection | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia sepsis | | | |
| subjects affected / exposed | 3 / 300 (1.00%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Escherichia urinary tract infection | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 300 (0.33%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastroenteritis | | | |
| subjects affected / exposed | 2 / 300 (0.67%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Gastroenteritis salmonella | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Herpes zoster | | | |
| subjects affected / exposed | 2 / 300 (0.67%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infection | | | |
| subjects affected / exposed | 3 / 300 (1.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infective exacerbation of chronic obstructive airways disease | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Influenza | | | |
| subjects affected / exposed | 2 / 300 (0.67%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Intervertebral discitis | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Klebsiella sepsis | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Listeria sepsis | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lower respiratory tract infection | | | |
| subjects affected / exposed | 6 / 300 (2.00%) | 4 / 150 (2.67%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 5 / 7 | 2 / 6 | 0 / 1 |
| deaths causally related to treatment / all | 1 / 1 | 1 / 2 | 0 / 0 |
| Lung infection | | | |
| subjects affected / exposed | 5 / 300 (1.67%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 4 / 9 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Meningitis | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Meningitis cryptococcal | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenic sepsis | | | |
| subjects affected / exposed | 3 / 300 (1.00%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ophthalmic herpes simplex | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ophthalmic herpes zoster | | | |

| | | | |
|---|-------------------|------------------|-----------------|
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumococcal bacteraemia | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumocystis jirovecii pneumonia | | | |
| subjects affected / exposed | 3 / 300 (1.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 2 / 3 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia | | | |
| subjects affected / exposed | 57 / 300 (19.00%) | 14 / 150 (9.33%) | 2 / 11 (18.18%) |
| occurrences causally related to treatment / all | 38 / 71 | 11 / 18 | 0 / 2 |
| deaths causally related to treatment / all | 3 / 5 | 1 / 3 | 0 / 0 |
| Pneumonia bacterial | | | |
| subjects affected / exposed | 2 / 300 (0.67%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia pneumococcal | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 2 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| Pneumonia pseudomonal | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 2 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| Pneumonia respiratory syncytial viral | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 0 / 150 (0.00%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia staphylococcal | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pneumonia streptococcal | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Progressive multifocal leukoencephalopathy | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pseudomonal bacteraemia | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pseudomonal sepsis | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory syncytial virus infection | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory tract infection | | | |
| subjects affected / exposed | 4 / 300 (1.33%) | 0 / 150 (0.00%) | 1 / 11 (9.09%) |
| occurrences causally related to treatment / all | 2 / 4 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Salmonella sepsis | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sepsis | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 7 / 300 (2.33%) | 3 / 150 (2.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 3 / 11 | 3 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 2 / 2 | 0 / 0 |
| Sepsis syndrome | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic arthritis streptococcal | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Septic shock | | | |
| subjects affected / exposed | 4 / 300 (1.33%) | 6 / 150 (4.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 2 / 5 | 3 / 6 | 0 / 0 |
| deaths causally related to treatment / all | 1 / 1 | 2 / 5 | 0 / 0 |
| Sialoadenitis | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sinusitis | | | |
| subjects affected / exposed | 2 / 300 (0.67%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin infection | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal cord infection | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Streptococcal infection | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Streptococcal sepsis | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subcutaneous abscess | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural empyema | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tooth infection | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 7 / 300 (2.33%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 2 / 8 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 5 / 150 (3.33%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urosepsis | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Metabolism and nutrition disorders | | | |
| Cachexia | | | |

| | | | |
|---|------------------|-----------------|----------------|
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| Decreased appetite | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dehydration | | | |
| subjects affected / exposed | 4 / 300 (1.33%) | 2 / 150 (1.33%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diabetic ketoacidosis | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypercalcaemia | | | |
| subjects affected / exposed | 13 / 300 (4.33%) | 5 / 150 (3.33%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 17 | 0 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperglycaemia | | | |
| subjects affected / exposed | 2 / 300 (0.67%) | 3 / 150 (2.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 1 / 2 | 3 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperuricaemia | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypokalaemia | | | |
| subjects affected / exposed | 2 / 300 (0.67%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyponatraemia | | | |

| | | | |
|---|-----------------|-----------------|----------------|
| subjects affected / exposed | 4 / 300 (1.33%) | 0 / 150 (0.00%) | 0 / 11 (0.00%) |
| occurrences causally related to treatment / all | 0 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| Non-serious adverse events | Pomalidomide Plus Low-Dose Dexamethasone | High-Dose Dexamethasone (BEFORE CROSSOVER) | High Dose Dexamethasone/Po malidomide (AFTER CROSSOVER) |
|---|--|---|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 291 / 300 (97.00%) | 143 / 150 (95.33%) | 11 / 11 (100.00%) |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 9 / 300 (3.00%) | 2 / 150 (1.33%) | 1 / 11 (9.09%) |
| occurrences (all) | 10 | 2 | 1 |
| Hot flush | | | |
| subjects affected / exposed | 2 / 300 (0.67%) | 2 / 150 (1.33%) | 1 / 11 (9.09%) |
| occurrences (all) | 2 | 2 | 1 |
| Hypotension | | | |
| subjects affected / exposed | 13 / 300 (4.33%) | 4 / 150 (2.67%) | 1 / 11 (9.09%) |
| occurrences (all) | 14 | 4 | 1 |
| Thrombophlebitis | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 0 | 1 |
| General disorders and administration site conditions | | | |
| Asthenia | | | |
| subjects affected / exposed | 53 / 300 (17.67%) | 25 / 150 (16.67%) | 1 / 11 (9.09%) |
| occurrences (all) | 76 | 42 | 1 |
| Chest pain | | | |
| subjects affected / exposed | 11 / 300 (3.67%) | 4 / 150 (2.67%) | 1 / 11 (9.09%) |
| occurrences (all) | 12 | 4 | 2 |
| Chills | | | |
| subjects affected / exposed | 18 / 300 (6.00%) | 2 / 150 (1.33%) | 0 / 11 (0.00%) |
| occurrences (all) | 20 | 2 | 0 |
| Fatigue | | | |

| | | | |
|---|--------------------|-------------------|-----------------|
| subjects affected / exposed | 103 / 300 (34.33%) | 40 / 150 (26.67%) | 3 / 11 (27.27%) |
| occurrences (all) | 200 | 82 | 5 |
| General physical health deterioration | | | |
| subjects affected / exposed | 17 / 300 (5.67%) | 5 / 150 (3.33%) | 0 / 11 (0.00%) |
| occurrences (all) | 19 | 5 | 0 |
| Influenza like illness | | | |
| subjects affected / exposed | 3 / 300 (1.00%) | 1 / 150 (0.67%) | 2 / 11 (18.18%) |
| occurrences (all) | 4 | 1 | 2 |
| Malaise | | | |
| subjects affected / exposed | 10 / 300 (3.33%) | 1 / 150 (0.67%) | 1 / 11 (9.09%) |
| occurrences (all) | 11 | 1 | 1 |
| Oedema | | | |
| subjects affected / exposed | 9 / 300 (3.00%) | 7 / 150 (4.67%) | 1 / 11 (9.09%) |
| occurrences (all) | 9 | 10 | 1 |
| Oedema peripheral | | | |
| subjects affected / exposed | 51 / 300 (17.00%) | 15 / 150 (10.00%) | 3 / 11 (27.27%) |
| occurrences (all) | 79 | 18 | 4 |
| Pyrexia | | | |
| subjects affected / exposed | 74 / 300 (24.67%) | 31 / 150 (20.67%) | 3 / 11 (27.27%) |
| occurrences (all) | 117 | 43 | 4 |
| Reproductive system and breast disorders | | | |
| Gynaecomastia | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 0 / 150 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 64 / 300 (21.33%) | 15 / 150 (10.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 85 | 16 | 1 |
| Dyspnoea | | | |
| subjects affected / exposed | 60 / 300 (20.00%) | 21 / 150 (14.00%) | 2 / 11 (18.18%) |
| occurrences (all) | 85 | 22 | 2 |
| Dyspnoea exertional | | | |
| subjects affected / exposed | 18 / 300 (6.00%) | 3 / 150 (2.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 22 | 3 | 0 |
| Epistaxis | | | |

| | | | |
|--|-------------------------|-------------------------|----------------------|
| subjects affected / exposed occurrences (all) | 26 / 300 (8.67%) 38 | 13 / 150 (8.67%) 18 | 1 / 11 (9.09%) 1 |
| Haemoptysis subjects affected / exposed occurrences (all) | 0 / 300 (0.00%) 0 | 2 / 150 (1.33%) 2 | 1 / 11 (9.09%) 1 |
| Productive cough subjects affected / exposed occurrences (all) | 5 / 300 (1.67%) 8 | 1 / 150 (0.67%) 1 | 1 / 11 (9.09%) 1 |
| Psychiatric disorders | | | |
| Agitation subjects affected / exposed occurrences (all) | 17 / 300 (5.67%) 20 | 7 / 150 (4.67%) 7 | 0 / 11 (0.00%) 0 |
| Anxiety subjects affected / exposed occurrences (all) | 15 / 300 (5.00%) 17 | 9 / 150 (6.00%) 12 | 0 / 11 (0.00%) 0 |
| Confusional state subjects affected / exposed occurrences (all) | 10 / 300 (3.33%) 12 | 7 / 150 (4.67%) 7 | 1 / 11 (9.09%) 1 |
| Delirium subjects affected / exposed occurrences (all) | 1 / 300 (0.33%) 1 | 0 / 150 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Insomnia subjects affected / exposed occurrences (all) | 36 / 300 (12.00%) 45 | 32 / 150 (21.33%) 41 | 0 / 11 (0.00%) 0 |
| Investigations | | | |
| Blood creatinine increased subjects affected / exposed occurrences (all) | 18 / 300 (6.00%) 34 | 6 / 150 (4.00%) 9 | 2 / 11 (18.18%) 6 |
| Blood thyroid stimulating hormone increased subjects affected / exposed occurrences (all) | 0 / 300 (0.00%) 0 | 1 / 150 (0.67%) 1 | 1 / 11 (9.09%) 1 |
| Neutrophil count decreased subjects affected / exposed occurrences (all) | 19 / 300 (6.33%) 92 | 1 / 150 (0.67%) 2 | 1 / 11 (9.09%) 2 |
| Weight decreased | | | |

| | | | |
|--|------------------|-----------------|-----------------|
| subjects affected / exposed | 15 / 300 (5.00%) | 5 / 150 (3.33%) | 2 / 11 (18.18%) |
| occurrences (all) | 17 | 5 | 2 |
| White blood cell count decreased | | | |
| subjects affected / exposed | 10 / 300 (3.33%) | 1 / 150 (0.67%) | 1 / 11 (9.09%) |
| occurrences (all) | 22 | 1 | 2 |
| Injury, poisoning and procedural complications | | | |
| Chillblains | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 0 / 150 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Contusion | | | |
| subjects affected / exposed | 5 / 300 (1.67%) | 2 / 150 (1.33%) | 1 / 11 (9.09%) |
| occurrences (all) | 5 | 3 | 1 |
| Fall | | | |
| subjects affected / exposed | 10 / 300 (3.33%) | 4 / 150 (2.67%) | 1 / 11 (9.09%) |
| occurrences (all) | 11 | 7 | 5 |
| Jaw fracture | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 0 / 150 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Ligament sprain | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 0 / 150 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Post-traumatic pain | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 0 / 150 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Rib fracture | | | |
| subjects affected / exposed | 7 / 300 (2.33%) | 2 / 150 (1.33%) | 1 / 11 (9.09%) |
| occurrences (all) | 8 | 3 | 1 |
| Skin abrasion | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 1 | 1 |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 7 / 300 (2.33%) | 4 / 150 (2.67%) | 1 / 11 (9.09%) |
| occurrences (all) | 7 | 4 | 1 |
| Nervous system disorders | | | |

| | | | |
|--------------------------------------|--------------------|-------------------|-----------------|
| Amnesia | | | |
| subjects affected / exposed | 2 / 300 (0.67%) | 0 / 150 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 2 | 0 | 1 |
| Burning sensation | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 1 / 150 (0.67%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 1 | 1 |
| Carpal tunnel syndrome | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 0 / 150 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 2 |
| Dizziness | | | |
| subjects affected / exposed | 40 / 300 (13.33%) | 13 / 150 (8.67%) | 0 / 11 (0.00%) |
| occurrences (all) | 53 | 13 | 0 |
| Headache | | | |
| subjects affected / exposed | 28 / 300 (9.33%) | 9 / 150 (6.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 38 | 9 | 1 |
| Lethargy | | | |
| subjects affected / exposed | 9 / 300 (3.00%) | 4 / 150 (2.67%) | 1 / 11 (9.09%) |
| occurrences (all) | 12 | 4 | 1 |
| Neuropathy peripheral | | | |
| subjects affected / exposed | 9 / 300 (3.00%) | 1 / 150 (0.67%) | 1 / 11 (9.09%) |
| occurrences (all) | 22 | 2 | 2 |
| Paraesthesia | | | |
| subjects affected / exposed | 12 / 300 (4.00%) | 6 / 150 (4.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 14 | 6 | 2 |
| Tremor | | | |
| subjects affected / exposed | 19 / 300 (6.33%) | 2 / 150 (1.33%) | 0 / 11 (0.00%) |
| occurrences (all) | 25 | 2 | 0 |
| Peripheral sensory neuropathy | | | |
| subjects affected / exposed | 26 / 300 (8.67%) | 4 / 150 (2.67%) | 2 / 11 (18.18%) |
| occurrences (all) | 56 | 10 | 4 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 159 / 300 (53.00%) | 77 / 150 (51.33%) | 4 / 11 (36.36%) |
| occurrences (all) | 434 | 158 | 8 |
| Leukopenia | | | |

| | | | |
|-----------------------------|--------------------|-------------------|-----------------|
| subjects affected / exposed | 40 / 300 (13.33%) | 8 / 150 (5.33%) | 0 / 11 (0.00%) |
| occurrences (all) | 102 | 29 | 0 |
| Lymphopenia | | | |
| subjects affected / exposed | 13 / 300 (4.33%) | 8 / 150 (5.33%) | 0 / 11 (0.00%) |
| occurrences (all) | 25 | 13 | 0 |
| Neutropenia | | | |
| subjects affected / exposed | 155 / 300 (51.67%) | 30 / 150 (20.00%) | 5 / 11 (45.45%) |
| occurrences (all) | 406 | 59 | 14 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 87 / 300 (29.00%) | 42 / 150 (28.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 251 | 120 | 4 |
| Ear and labyrinth disorders | | | |
| Ear pain | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 0 / 150 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 8 / 300 (2.67%) | 4 / 150 (2.67%) | 1 / 11 (9.09%) |
| occurrences (all) | 10 | 4 | 2 |
| Macular pigmentation | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 0 / 150 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastrointestinal disorders | | | |
| Abdominal pain upper | | | |
| subjects affected / exposed | 8 / 300 (2.67%) | 3 / 150 (2.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 10 | 3 | 1 |
| Constipation | | | |
| subjects affected / exposed | 72 / 300 (24.00%) | 22 / 150 (14.67%) | 1 / 11 (9.09%) |
| occurrences (all) | 108 | 26 | 1 |
| Diarrhoea | | | |
| subjects affected / exposed | 73 / 300 (24.33%) | 26 / 150 (17.33%) | 3 / 11 (27.27%) |
| occurrences (all) | 123 | 32 | 4 |
| Epigastric discomfort | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 0 / 150 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Mouth ulceration | | | |

| | | | |
|--|-------------------|-------------------|-----------------|
| subjects affected / exposed | 3 / 300 (1.00%) | 2 / 150 (1.33%) | 1 / 11 (9.09%) |
| occurrences (all) | 3 | 2 | 1 |
| Nausea | | | |
| subjects affected / exposed | 57 / 300 (19.00%) | 16 / 150 (10.67%) | 3 / 11 (27.27%) |
| occurrences (all) | 82 | 17 | 3 |
| Parotid gland enlargement | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 0 / 150 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Vomiting | | | |
| subjects affected / exposed | 25 / 300 (8.33%) | 6 / 150 (4.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 31 | 6 | 1 |
| Hepatobiliary disorders | | | |
| Cholelithiasis | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 0 | 1 |
| Skin and subcutaneous tissue disorders | | | |
| Blister | | | |
| subjects affected / exposed | 1 / 300 (0.33%) | 0 / 150 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 1 | 0 | 1 |
| Dry skin | | | |
| subjects affected / exposed | 8 / 300 (2.67%) | 3 / 150 (2.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 8 | 3 | 1 |
| Erythema | | | |
| subjects affected / exposed | 8 / 300 (2.67%) | 2 / 150 (1.33%) | 1 / 11 (9.09%) |
| occurrences (all) | 9 | 2 | 1 |
| Hyperhidrosis | | | |
| subjects affected / exposed | 18 / 300 (6.00%) | 1 / 150 (0.67%) | 0 / 11 (0.00%) |
| occurrences (all) | 23 | 2 | 0 |
| Hyperkeratosis | | | |
| subjects affected / exposed | 0 / 300 (0.00%) | 0 / 150 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 0 | 0 | 1 |
| Pruritus | | | |
| subjects affected / exposed | 22 / 300 (7.33%) | 4 / 150 (2.67%) | 1 / 11 (9.09%) |
| occurrences (all) | 26 | 4 | 1 |
| Rash | | | |

| | | | |
|---|-------------------------|-------------------------|----------------------|
| subjects affected / exposed occurrences (all) | 25 / 300 (8.33%) 40 | 1 / 150 (0.67%) 1 | 1 / 11 (9.09%) 1 |
| Rash papular subjects affected / exposed occurrences (all) | 1 / 300 (0.33%) 1 | 0 / 150 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Swelling face subjects affected / exposed occurrences (all) | 2 / 300 (0.67%) 2 | 4 / 150 (2.67%) 4 | 1 / 11 (9.09%) 1 |
| Renal and urinary disorders Acute kidney injury subjects affected / exposed occurrences (all) | 5 / 300 (1.67%) 5 | 3 / 150 (2.00%) 4 | 1 / 11 (9.09%) 3 |
| Nocturia subjects affected / exposed occurrences (all) | 1 / 300 (0.33%) 2 | 0 / 150 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Endocrine disorders Adrenal insufficiency subjects affected / exposed occurrences (all) | 2 / 300 (0.67%) 2 | 1 / 150 (0.67%) 1 | 1 / 11 (9.09%) 1 |
| Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all) | 28 / 300 (9.33%) 35 | 7 / 150 (4.67%) 8 | 0 / 11 (0.00%) 0 |
| Back pain subjects affected / exposed occurrences (all) | 59 / 300 (19.67%) 69 | 23 / 150 (15.33%) 25 | 2 / 11 (18.18%) 4 |
| Bone pain subjects affected / exposed occurrences (all) | 54 / 300 (18.00%) 71 | 20 / 150 (13.33%) 27 | 2 / 11 (18.18%) 6 |
| Coccydynia subjects affected / exposed occurrences (all) | 0 / 300 (0.00%) 0 | 0 / 150 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Muscle spasms subjects affected / exposed occurrences (all) | 47 / 300 (15.67%) 68 | 11 / 150 (7.33%) 12 | 1 / 11 (9.09%) 3 |
| Muscular weakness | | | |

| | | | |
|-----------------------------|-------------------|-------------------|-----------------|
| subjects affected / exposed | 11 / 300 (3.67%) | 18 / 150 (12.00%) | 2 / 11 (18.18%) |
| occurrences (all) | 17 | 29 | 3 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 18 / 300 (6.00%) | 5 / 150 (3.33%) | 0 / 11 (0.00%) |
| occurrences (all) | 19 | 5 | 0 |
| Musculoskeletal chest pain | | | |
| subjects affected / exposed | 12 / 300 (4.00%) | 3 / 150 (2.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 14 | 3 | 1 |
| Myalgia | | | |
| subjects affected / exposed | 12 / 300 (4.00%) | 4 / 150 (2.67%) | 1 / 11 (9.09%) |
| occurrences (all) | 14 | 4 | 1 |
| Myopathy | | | |
| subjects affected / exposed | 4 / 300 (1.33%) | 11 / 150 (7.33%) | 0 / 11 (0.00%) |
| occurrences (all) | 11 | 24 | 0 |
| Osteolysis | | | |
| subjects affected / exposed | 2 / 300 (0.67%) | 0 / 150 (0.00%) | 1 / 11 (9.09%) |
| occurrences (all) | 2 | 0 | 1 |
| Pain in extremity | | | |
| subjects affected / exposed | 21 / 300 (7.00%) | 9 / 150 (6.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 29 | 10 | 0 |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 34 / 300 (11.33%) | 7 / 150 (4.67%) | 1 / 11 (9.09%) |
| occurrences (all) | 51 | 7 | 1 |
| Cellulitis | | | |
| subjects affected / exposed | 6 / 300 (2.00%) | 2 / 150 (1.33%) | 1 / 11 (9.09%) |
| occurrences (all) | 8 | 2 | 2 |
| Herpes zoster | | | |
| subjects affected / exposed | 6 / 300 (2.00%) | 1 / 150 (0.67%) | 1 / 11 (9.09%) |
| occurrences (all) | 6 | 1 | 1 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 30 / 300 (10.00%) | 1 / 150 (0.67%) | 1 / 11 (9.09%) |
| occurrences (all) | 44 | 1 | 1 |
| Pneumonia | | | |
| subjects affected / exposed | 19 / 300 (6.33%) | 5 / 150 (3.33%) | 0 / 11 (0.00%) |
| occurrences (all) | 20 | 5 | 0 |

| | | | |
|---|-------------------------|------------------------|----------------------|
| Respiratory tract infection subjects affected / exposed occurrences (all) | 15 / 300 (5.00%) 16 | 5 / 150 (3.33%) 5 | 0 / 11 (0.00%) 0 |
| Sinusitis subjects affected / exposed occurrences (all) | 10 / 300 (3.33%) 12 | 4 / 150 (2.67%) 5 | 1 / 11 (9.09%) 1 |
| Tooth abscess subjects affected / exposed occurrences (all) | 1 / 300 (0.33%) 1 | 1 / 150 (0.67%) 1 | 1 / 11 (9.09%) 1 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 47 / 300 (15.67%) 80 | 10 / 150 (6.67%) 10 | 2 / 11 (18.18%) 5 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 18 / 300 (6.00%) 29 | 6 / 150 (4.00%) 9 | 2 / 11 (18.18%) 3 |
| Wound infection subjects affected / exposed occurrences (all) | 0 / 300 (0.00%) 0 | 0 / 150 (0.00%) 0 | 1 / 11 (9.09%) 1 |
| Metabolism and nutrition disorders | | | |
| Decreased appetite subjects affected / exposed occurrences (all) | 40 / 300 (13.33%) 46 | 10 / 150 (6.67%) 11 | 3 / 11 (27.27%) 3 |
| Dehydration subjects affected / exposed occurrences (all) | 14 / 300 (4.67%) 16 | 8 / 150 (5.33%) 9 | 0 / 11 (0.00%) 0 |
| Hypercalcaemia subjects affected / exposed occurrences (all) | 11 / 300 (3.67%) 14 | 11 / 150 (7.33%) 16 | 0 / 11 (0.00%) 0 |
| Hypocalcaemia subjects affected / exposed occurrences (all) | 14 / 300 (4.67%) 34 | 9 / 150 (6.00%) 10 | 0 / 11 (0.00%) 0 |
| Hyperglycaemia subjects affected / exposed occurrences (all) | 18 / 300 (6.00%) 34 | 10 / 150 (6.67%) 14 | 0 / 11 (0.00%) 0 |
| Hypokalaemia | | | |

| | | | |
|-----------------------------|-------------------|------------------|----------------|
| subjects affected / exposed | 31 / 300 (10.33%) | 12 / 150 (8.00%) | 0 / 11 (0.00%) |
| occurrences (all) | 57 | 17 | 0 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-----------------|---|
| 14 October 2010 | Amendment 1 implemented the following significant changes: - The comparator treatment (Treatment Arm B) was changed from LD-dex to HD-dex. - As a direct result of the above change, the study design was changed from placebo-controlled and double-blind to active-controlled and open-label. Placebo was no longer administered in Treatment Arm B. - For the purpose of sample size calculation, the estimated median PFS was amended from 6 - 9 months to 5 - 7.5 months, to be more in agreement with median PFS seen in patients treated with HD-dex (i.e., approximately 5 months). |
| 12 June 2011 | Amendment 2 implemented the following significant changes: - Required SPMs be treated as SAEs and reported throughout the study, including LTFU, until death or 5 years after randomization, whichever occurred first. - Added Canada as a region in which the study would be conducted. - Expanded the PK sub-study from 30 subjects to all subjects who consented to sampling at select sites. - Required confirmation of investigator-assessed PD by IRAC for all subjects in both treatment arms. - Added collection of blood, bone marrow, serum, and saliva to assess the mechanism of action of pomalidomide or identify possible markers that correlate with response, including genetic aberrations. - Updated inclusion criterion to lower the eligibility requirement for measurable level of serum M-protein from 1.0 g/dL to 0.5 g/dL. - Updated exclusion criterion for serum total bilirubin to allow for higher level at study entry for subjects with hereditary enzymatic disorders such as Gilbert syndrome, glucose-6-phosphate dehydrogenase deficiency, etc. - Specified that \geq Grade 3 rash during prior thalidomide or lenalidomide was considered hypersensitivity. - Updated language so that subjects with prior allogeneic bone marrow or allogeneic peripheral blood stem cell transplant may have been included if at least 12 months had elapsed since their transplant or if they were not on concomitant immunosuppressive mediations related to the transplant at study entry. - Allowed for collection of minimal data if available, during LTFU for subjects who discontinued the study treatment phase prior to progression. - Updated pregnancy prevention and testing requirement language to match the Pregnancy Prevention Risk Management Plan. - Updated to state only subjects randomized to Pom+LD-dex would be maintained in pregnancy pomalidomide pregnancy prevention programs. |

| | |
|------------------|--|
| 04 November 2011 | Amendment 3 implemented the following significant changes: - Added 1 site in the US - Required that exclusion criterion #2 reflect the exclusion of subjects with prior history of malignancies, other than MM, unless the subject had been free of the disease for ≥ 5 years instead of ≥ 3 years. - Updated screening requirements to reflect that, in addition to the use of growth factors, the use of platelet and/or RBC transfusions was to be allowed throughout the study, including the screening period, at the discretion of the investigator. However, subjects who failed screening as a result of neutropenia, thrombocytopenia, or anemia were not permitted to use growth factors, platelet or RBC transfusions to become eligible. - Updated to reflect that, for subjects who had a creatinine clearance less than 45 mL/min by the Cockcroft-Gault method at Screening and/or Cycle 1 Day 1, an evaluation of creatinine clearance would be performed using the 24-hour urine sample from the urine M-Protein collection. The Cockcroft-Gault method was to be used for the remainder of the study. - Clarified that after screening, a bone marrow aspirate and/or biopsy should be repeated to confirm CR and may also have been done when clinically indicated to confirm PD. - Updated inclusion criterion #8 regarding prior alkylator exposure. In addition to receiving adequate alkylator exposure as a part of SCT or minimum of 6 consecutive cycles of an alkylator based therapy, subjects may also have qualified for the study if progression on treatment with an alkylator occurred, provided that the subject received at least 2 cycles of an alkylator-containing therapy. - Updated exclusion criterion #7 to reflect that subjects who had not discontinued immunosuppressive treatment for at least 4 weeks prior to initiation of study treatment (rather than 12 months) and were currently dependent on such treatment would not be eligible for the study. |
| 08 November 2012 | - The Independent Data Monitoring Committee (IDMC) had reviewed the data related to the final PFS analysis and interim OS survival analysis. The PFS was statistically significant in favor of the pomalidomide and low-dose dexamethasone arm and the O'Brien-Fleming upper superiority boundary was crossed for overall survival. Accordingly, the IDMC recommended that subjects who were still on the high dose dexamethasone treatment should be permitted to receive pomalidomide with or without LD-dex treatment at the discretion of the Investigator. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported