



Clinical trial results:

A Phase-3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study To Compare Efficacy and Safety of Pomalidomide in subjects With Myeloproliferative Neoplasm-Associated Myelofibrosis and Red Blood Cell-Transfusion-Dependence

Summary

| | |
|--------------------------|----------------------------|
| EudraCT number | 2010-018965-42 |
| Trial protocol | GB DE NL AT IT ES BE SE PL |
| Global end of trial date | 14 May 2018 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v2 (current) |
| This version publication date | 13 July 2019 |
| First version publication date | 31 May 2019 |
| Version creation reason | |

Trial information

Trial identification

| | |
|-----------------------|----------------|
| Sponsor protocol code | CC-4047-MF-002 |
|-----------------------|----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT01178281 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|--|
| Sponsor organisation name | Celgene Corporation |
| Sponsor organisation address | 87 Morris Avenue, Summit, United States, 07901 |
| Public contact | Clinical Trial Disclosure, Celgene Corporation, 01 888-260-1599, ClinicalTrialDisclosure@Celgene.com |
| Scientific contact | Robert Peter Gale, MD, PhD, Celgene Corporation, 01 908 656 0484, RGale@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 | 14 May 2018 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 14 May 2018 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The objective of this study is to determine whether pomalidomide is safe and effective in reversing red blood cell (RBC)-transfusion-dependence in persons with myeloproliferative neoplasm (MPN)-associated myelofibrosis (global study) and in reversing anemia in Chinese with MPN-associated myelofibrosis and severe anemia not receiving RBC-transfusions (China extension study only).

Protection of trial subjects:

Protection of Patient Confidentiality, Archiving of Essential Documents

Background therapy: -

Evidence for comparator: -

| | |
|---|-------------------|
| Actual start date of recruitment | 07 September 2010 |
| Long term follow-up planned | Yes |
| Long term follow-up rationale | Safety, Efficacy |
| 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 | Australia: 3 |
| Country: Number of subjects enrolled | Austria: 9 |
| Country: Number of subjects enrolled | Belgium: 11 |
| Country: Number of subjects enrolled | Canada: 8 |
| Country: Number of subjects enrolled | China: 36 |
| Country: Number of subjects enrolled | France: 21 |
| Country: Number of subjects enrolled | Germany: 9 |
| Country: Number of subjects enrolled | Italy: 36 |
| Country: Number of subjects enrolled | Japan: 9 |
| Country: Number of subjects enrolled | Netherlands: 7 |
| Country: Number of subjects enrolled | Russian Federation: 13 |
| Country: Number of subjects enrolled | Spain: 6 |
| Country: Number of subjects enrolled | Sweden: 6 |
| Country: Number of subjects enrolled | United Kingdom: 18 |
| Country: Number of subjects enrolled | United States: 75 |
| Worldwide total number of subjects | 267 |
| EEA total number of subjects | 123 |

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) | 91 |
| From 65 to 84 years | 172 |
| 85 years and over | 4 |

Subject disposition

Recruitment

Recruitment details:

Participants in the global study were enrolled at 72 clinical centers in 15 countries. In addition, the China-specific extension study enrolled participants with myeloproliferative neoplasm (MPN)-associated myelofibrosis and severe anemia not receiving red blood cell (RBC)-transfusions at 5 sites in China.

Pre-assignment

Screening details:

Participants in the global study were randomized 2:1 to receive blinded pomalidomide or placebo. All participants in the China extension received open-label pomalidomide. Randomization was stratified by age (\leq vs >65 years), white blood cells ($<$ or $\geq 25 \times 10/L$), and baseline transfusion requirement (\leq vs >4 units RBC/28 days over the prior 84 days).

Period 1

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

Arms

| | |
|------------------------------|---------------------|
| Are arms mutually exclusive? | Yes |
| Arm title | Pomalidomide 0.5 mg |

Arm description:

Participants received pomalidomide 0.5 mg/day by mouth for at least 168 days unless there were unacceptable side effects or disease progression. Participants who were RBC-transfusion independent or experienced clinical benefit (defined as a reduction from Baseline of $\geq 50\%$ in RBC-transfusion frequency during the prior 84-day interval) could continue to receive pomalidomide until loss of RBC-transfusion independence response or clinical benefit, or other criteria for treatment discontinuation applied.

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

Dosage and administration details:

Pomalidomide 0.5 mg by mouth once daily

| | |
|------------------|---------|
| Arm title | Placebo |
|------------------|---------|

Arm description:

Participants received placebo taken by mouth once daily for at least 168 days unless there were unacceptable side effects or disease progression. Participants who were RBC-transfusion independent or experienced clinical benefit could continue to receive placebo until loss of RBC-transfusion independence response or clinical benefit, or other criteria for treatment discontinuation applied.

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

Dosage and administration details:

Placebo capsules by mouth once daily

| | |
|------------------|--------------------------------------|
| Arm title | China Extension: Pomalidomide 0.5 mg |
|------------------|--------------------------------------|

Arm description:

Participants received pomalidomide 0.5 mg/day by mouth for at least 168 days unless there were unacceptable side effects, disease progression, or they received a RBC-transfusion. Participants who experienced anemia response could continue treatment until the response was lost or other criteria for treatment discontinuation applied. Participants enrolled in the China extension study were not blinded.

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

Dosage and administration details:

Pomalidomide 0.5 mg by mouth once daily

| Number of subjects in period 1 | Pomalidomide 0.5 mg | Placebo | China Extension: Pomalidomide 0.5 mg |
|---------------------------------------|---------------------|-------------------|--------------------------------------|
| | | | |
| Started | 168 | 84 | 15 |
| Received Study Drug | 167 ^[1] | 83 ^[2] | 15 |
| Completed | 168 | 84 | 15 |

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: Completed indicates participants no longer on-study

[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: Completed indicates participants no longer on-study

Baseline characteristics

Reporting groups

| | |
|---|--------------------------------------|
| Reporting group title | Pomalidomide 0.5 mg |
| Reporting group description: | |
| Participants received pomalidomide 0.5 mg/day by mouth for at least 168 days unless there were unacceptable side effects or disease progression. Participants who were RBC-transfusion independent or experienced clinical benefit (defined as a reduction from Baseline of $\geq 50\%$ in RBC-transfusion frequency during the prior 84-day interval) could continue to receive pomalidomide until loss of RBC-transfusion independence response or clinical benefit, or other criteria for treatment discontinuation applied. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Participants received placebo taken by mouth once daily for at least 168 days unless there were unacceptable side effects or disease progression. Participants who were RBC-transfusion independent or experienced clinical benefit could continue to receive placebo until loss of RBC-transfusion independence response or clinical benefit, or other criteria for treatment discontinuation applied. | |
| Reporting group title | China Extension: Pomalidomide 0.5 mg |
| Reporting group description: | |
| Participants received pomalidomide 0.5 mg/day by mouth for at least 168 days unless there were unacceptable side effects, disease progression, or they received a RBC-transfusion. Participants who experienced anemia response could continue treatment until the response was lost or other criteria for treatment discontinuation applied. Participants enrolled in the China extension study were not blinded. | |

| Reporting group values | Pomalidomide 0.5 mg | Placebo | China Extension: Pomalidomide 0.5 mg |
|---|---------------------|--------------|--------------------------------------|
| Number of subjects | 168 | 84 | 15 |
| Age categorical Units: Subjects | | | |
| Adults (18-64 years) | 55 | 26 | 10 |
| From 65-84 years | 109 | 58 | 5 |
| 85 years and over | 4 | 0 | 0 |
| Age Continuous Units: years | | | |
| median | 69.0 | 69.0 | 63.0 |
| full range (min-max) | 40.0 to 90.0 | 44.0 to 81.0 | 41.0 to 76.0 |
| Gender, Male/Female Units: Subjects | | | |
| Female | 41 | 28 | 6 |
| Male | 127 | 56 | 9 |
| Ethnicity (NIH/OMB) Units: Subjects | | | |
| Hispanic or Latino | 3 | 1 | 0 |
| Not Hispanic or Latino | 144 | 79 | 15 |
| Unknown or Not Reported | 21 | 4 | 0 |
| Race/Ethnicity, Customized Units: Subjects | | | |
| American Indian or Alaskan Native | 1 | 0 | 0 |
| Asian | 20 | 11 | 15 |
| Black or African American | 2 | 3 | 0 |
| Native Hawaiian or Other Pacific Islanders | 1 | 0 | 0 |

| | | | |
|---|-------------|-------------|------------|
| White | 122 | 66 | 0 |
| Other | 3 | 0 | 0 |
| Missing | 19 | 4 | 0 |
| Eastern Cooperative Oncology Group (ECOG) Performance Status | | | |
| ECOG performance status is used to describe a patient's level of functioning in terms of their ability to care for themselves, daily activity, and physical ability (walking, working, etc.). The scale ranges from 0 to 5: 0 = Fully active, no restrictions; 1= Restricted activity but ambulatory, able to carry out work of a light nature; 2= Ambulatory and capable of all self-care but unable to carry out work activities; 3= Limited self-care, confined to bed or chair more than 50% of waking hours; 4= Completely disabled, no self-care, confined to bed or chair; 5= Dead | | | |
| Units: Subjects | | | |
| 0 (Fully active) | 53 | 22 | 5 |
| 1 (Restrictive but ambulatory) | 85 | 47 | 9 |
| 2 (Ambulatory but unable to work) | 30 | 15 | 1 |
| 3 (Limited self care) | 0 | 0 | 0 |
| 4 (Completely disabled) | 0 | 0 | 0 |
| Disease sub-type | | | |
| Units: Subjects | | | |
| Primary myelofibrosis | 127 | 65 | 10 |
| Post-polycythemia vera myelofibrosis | 17 | 8 | 2 |
| Post-essential thrombocythemia myelofibrosis | 23 | 11 | 3 |
| Missing | 1 | 0 | 0 |
| Baseline RBC Transfusion Burden | | | |
| Defined as the average number of RBC-transfusion-units per 28 days over the 84 days immediately prior to randomization. | | | |
| Units: units per 28 days | | | |
| median | 2.7 | 2.8 | 0.0 |
| full range (min-max) | 1.3 to 13.3 | 1.3 to 10.0 | 0.0 to 0.0 |

| | | | |
|-------------------------------|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 267 | | |
| Age categorical | | | |
| Units: Subjects | | | |
| Adults (18-64 years) | 91 | | |
| From 65-84 years | 172 | | |
| 85 years and over | 4 | | |
| Age Continuous | | | |
| Units: years | | | |
| median | | | |
| full range (min-max) | - | | |
| Gender, Male/Female | | | |
| Units: Subjects | | | |
| Female | 75 | | |
| Male | 192 | | |
| Ethnicity (NIH/OMB) | | | |
| Units: Subjects | | | |
| Hispanic or Latino | 4 | | |
| Not Hispanic or Latino | 238 | | |
| Unknown or Not Reported | 25 | | |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |

| | | | |
|---|-----|--|--|
| American Indian or Alaskan Native | 1 | | |
| Asian | 46 | | |
| Black or African American | 5 | | |
| Native Hawaiian or Other Pacific Islanders | 1 | | |
| White | 188 | | |
| Other | 3 | | |
| Missing | 23 | | |
| Eastern Cooperative Oncology Group (ECOG) Performance Status | | | |
| ECOG performance status is used to describe a patient's level of functioning in terms of their ability to care for themselves, daily activity, and physical ability (walking, working, etc.). The scale ranges from 0 to 5: 0 = Fully active, no restrictions; 1= Restricted activity but ambulatory, able to carry out work of a light nature; 2= Ambulatory and capable of all self-care but unable to carry out work activities; 3= Limited self-care, confined to bed or chair more than 50% of waking hours; 4= Completely disabled, no self-care, confined to bed or chair; 5= Dead | | | |
| Units: Subjects | | | |
| 0 (Fully active) | 80 | | |
| 1 (Restrictive but ambulatory) | 141 | | |
| 2 (Ambulatory but unable to work) | 46 | | |
| 3 (Limited self care) | 0 | | |
| 4 (Completely disabled) | 0 | | |
| Disease sub-type | | | |
| Units: Subjects | | | |
| Primary myelofibrosis | 202 | | |
| Post-polycythemia vera myelofibrosis | 27 | | |
| Post-essential thrombocythemia myelofibrosis | 37 | | |
| Missing | 1 | | |
| Baseline RBC Transfusion Burden | | | |
| Defined as the average number of RBC-transfusion-units per 28 days over the 84 days immediately prior to randomization. | | | |
| Units: units per 28 days | | | |
| median | | | |
| full range (min-max) | - | | |

End points

End points reporting groups

| | |
|---|--------------------------------------|
| Reporting group title | Pomalidomide 0.5 mg |
| Reporting group description: Participants received pomalidomide 0.5 mg/day by mouth for at least 168 days unless there were unacceptable side effects or disease progression. Participants who were RBC-transfusion independent or experienced clinical benefit (defined as a reduction from Baseline of $\geq 50\%$ in RBC-transfusion frequency during the prior 84-day interval) could continue to receive pomalidomide until loss of RBC-transfusion independence response or clinical benefit, or other criteria for treatment discontinuation applied. | |
| Reporting group title | Placebo |
| Reporting group description: Participants received placebo taken by mouth once daily for at least 168 days unless there were unacceptable side effects or disease progression. Participants who were RBC-transfusion independent or experienced clinical benefit could continue to receive placebo until loss of RBC-transfusion independence response or clinical benefit, or other criteria for treatment discontinuation applied. | |
| Reporting group title | China Extension: Pomalidomide 0.5 mg |
| Reporting group description: Participants received pomalidomide 0.5 mg/day by mouth for at least 168 days unless there were unacceptable side effects, disease progression, or they received a RBC-transfusion. Participants who experienced anemia response could continue treatment until the response was lost or other criteria for treatment discontinuation applied. Participants enrolled in the China extension study were not blinded. | |

Primary: China Extension: Number of Participants Achieving a Hemoglobin Increase of ≥ 15 g/L Compared to Baseline for ≥ 84 Consecutive Days

| | |
|---|--|
| End point title | China Extension: Number of Participants Achieving a Hemoglobin Increase of ≥ 15 g/L Compared to Baseline for ≥ 84 Consecutive Days ^{[1][2]} |
| End point description: A response in the China extension study was defined as an increase in hemoglobin ≥ 15 g/L above baseline value (in the absence of RBC transfusion) for ≥ 84 consecutive days. The analysis was conducted in the China extension intent-to-treat (ITT) population which included all participants enrolled in the China extension study. | |
| End point type | Primary |
| End point timeframe: From the first dose of study drug until treatment discontinuation; median treatment duration was 24.0 weeks. | |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Endpoint was analyzed in the global study population only

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Endpoint was analyzed in the global study population only

| | | | | |
|-----------------------------|--------------------------------------|--|--|--|
| End point values | China Extension: Pomalidomide 0.5 mg | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 15 | | | |
| Units: Participants | 1 | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants who Achieved RBC-Transfusion Independence

| | |
|-----------------|---|
| End point title | Percentage of Participants who Achieved RBC-Transfusion Independence ^[3] |
|-----------------|---|

End point description:

RBC-transfusion independence was defined as the absence of RBC transfusions for any consecutive 84-day interval. The analysis was conducted in the global study intent-to-treat (ITT) population which included all randomized participants.

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

End point timeframe:

168 days

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Endpoint was analyzed in the global study population only

| | | | | |
|-----------------------------------|-----------------------|----------------------|--|--|
| End point values | Pomalidomide 0.5 mg | Placebo | | |
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 168 | 84 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 17.3 (11.88 to 23.84) | 16.7 (9.42 to 26.38) | | |

Statistical analyses

| | |
|---|-------------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Pomalidomide 0.5 mg v Placebo |
| Number of subjects included in analysis | 252 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 1 |
| Method | Fisher exact |

Secondary: Overall Survival

| | |
|-----------------|---------------------------------|
| End point title | Overall Survival ^[4] |
|-----------------|---------------------------------|

End point description:

The time from randomization to the death or to the latest date when participants were known to be alive. Overall survival was analyzed in the global study intent-to-treat population using the Kaplan-Meier method; participants who were alive or lost to follow-up were censored at the latest date they were

known to be alive.

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

End point timeframe:

From first dose of study drug up to end of study; median follow-up time was 19.1 months in the pomalidomide 0.5 mg arm and 17.6 months in the placebo arm.

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Endpoint was analyzed in the global study population only

| End point values | Pomalidomide 0.5 mg | Placebo | | |
|----------------------------------|---------------------|---------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 168 | 84 | | |
| Units: months | | | | |
| median (confidence interval 95%) | 24.2 (19.5 to 33.5) | 26.2 (18.0 to 32.6) | | |

Statistical analyses

| | |
|---|-------------------------------|
| Statistical analysis title | Statistical Analysis 1 |
| Comparison groups | Pomalidomide 0.5 mg v Placebo |
| Number of subjects included in analysis | 252 |
| Analysis specification | Pre-specified |
| Analysis type | other |
| P-value | = 0.929 |
| Method | Logrank |

Secondary: Duration of RBC-Transfusion Independence

| | |
|-----------------|---|
| End point title | Duration of RBC-Transfusion Independence ^[5] |
|-----------------|---|

End point description:

The duration of RBC-transfusion independence is the time from the date at which the first RBC-transfusion independence started to the date of another RBC-transfusion given at least 84 days after the time the transfusion independence started. The duration of RBC-transfusion independence was analyzed in the global study intent-to-treat population who had an RBC-transfusion independence response using the Kaplan-Meier method. Data were censored at the end of the treatment phase for participants who had not received another RBC-transfusion after the start of transfusion independence by the end of treatment phase. "99999" indicates data that were not estimable.

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

End point timeframe:

From first dose of study drug up to 28 days after last dose, as of the data cut-off date of 16 Jan 2013; Median treatment duration was 23.6 weeks in the pomalidomide arm and 23.9 weeks in the placebo arm.

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Endpoint was analyzed in the global study population only

| End point values | Pomalidomide 0.5 mg | Placebo | | |
|----------------------------------|------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 ^[6] | 14 ^[7] | | |
| Units: months | | | | |
| median (confidence interval 95%) | 99999 (4.8 to 99999) | 5.8 (3.0 to 99999) | | |

Notes:

[6] - Participants with an RBC-transfusion independence response

[7] - Participants with an RBC-transfusion independence response

Statistical analyses

No statistical analyses for this end point

Secondary: Time to RBC-Transfusion Independence

| | |
|-----------------|---|
| End point title | Time to RBC-Transfusion Independence ^[8] |
|-----------------|---|

End point description:

Time to response was measured from first dose of study drug to the start of the first response. The start date of the response was defined as one day after the last date of an RBC-transfusion for participants who received a transfusion after the first dose, and as the date of the first dose of study drug for participants who received no transfusions during the 84 days after the first dose of study drug.

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

End point timeframe:

From first dose of study drug up to 28 days after last dose, as of the data cut-off date of 16 Jan 2013; median treatment duration was 23.6 weeks in the pomalidomide arm and 23.9 weeks in the placebo arm.

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period. Justification: Endpoint was analyzed in the global study population only

| End point values | Pomalidomide 0.5 mg | Placebo | | |
|-------------------------------|------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 29 ^[9] | 14 ^[10] | | |
| Units: weeks | | | | |
| median (full range (min-max)) | 6.9 (0.1 to 20.1) | 2.4 (0.1 to 15.4) | | |

Notes:

[9] - Participants with an RBC-transfusion independence response

[10] - Participants with an RBC-transfusion independence response

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Treatment-emergent Adverse Events

| | |
|-----------------|---|
| End point title | Number of Participants with Treatment-emergent Adverse Events |
|-----------------|---|

End point description:

A TEAE is an adverse event (AE) that starts on or after the first dose of study drug. The severity of each AE was graded according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 and according to the following scale: Grade 1 = Mild (transient or mild discomfort; no limitation in activity; no medical intervention/therapy required); Grade 2 = Moderate (mild to moderate limitation in activity, some assistance may be needed; minimal medical intervention/therapy required); Grade 3 = Severe (marked limitation in activity, assistance usually

required; medical intervention/therapy required, hospitalization possible); Grade 4 = Life-threatening (extreme limitation in activity, significant assistance or medical intervention/therapy required, hospitalization or hospice care probable); Grade 5 = Death Drug-related (related) AEs are those suspected by the Investigator as being related to administration of study drug.

| | |
|---|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From the first dose of study drug until 28 days after last dose; median treatment duration was 23.7 weeks in the pomalidomide arm, 23.9 weeks in the placebo arm, and 24.0 weeks in the China extension pomalidomide arm. | |

| End point values | Pomalidomide 0.5 mg | Placebo | China Extension: Pomalidomide 0.5 mg | |
|--|------------------------|-----------------|---|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 167 | 83 | 15 | |
| Units: Participants | | | | |
| Any adverse event (AE) | 164 | 81 | 12 | |
| Adverse event suspected as related to study drug | 90 | 32 | 3 | |
| Adverse event leading to dose interruption | 48 | 17 | 2 | |
| Drug-related AE leading to dose interruption | 26 | 6 | 1 | |
| AE leading to discontinuation of study drug | 53 | 14 | 0 | |
| Related AE leading to study drug discontinuation | 21 | 8 | 0 | |
| Grade 3/4 adverse event | 100 | 44 | 4 | |
| Grade 3/4 AE related to study drug | 45 | 13 | 0 | |
| Grade 3/4 AE leading to study drug discontinuation | 33 | 9 | 0 | |
| Grade 3/4 AE leading to dose interruption | 36 | 14 | 1 | |
| Grade 5 adverse event | 17 | 10 | 0 | |
| Grade 5 AE related to study drug | 1 | 3 | 0 | |
| Serious adverse event (SAE) | 76 | 29 | 0 | |
| SAE related to study drug | 24 | 7 | 0 | |
| SAE leading to discontinuation of study drug | 31 | 8 | 0 | |
| SAE leading to dose interruption | 22 | 7 | 0 | |

Statistical analyses

No statistical analyses for this end point

Secondary: Healthcare Resource Utilization

| | |
|--|---|
| End point title | Healthcare Resource Utilization ^[11] |
| End point description: | |
| Characterization of medical resource utilization among participants treated with pomalidomide as compared to participants receiving placebo treatment. | |
| End point type | Secondary |

End point timeframe:

From first dose of study drug up to 28 days after last dose, as of the data cut-off date of 16 Jan 2013; Median treatment duration was 23.6 weeks in the pomalidomide arm and 23.9 weeks in the placebo arm.

Notes:

[11] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: There was no data collected for healthcare resource utilization

| End point values | Pomalidomide 0.5 mg | Placebo | | |
|-----------------------------|------------------------|-------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 0 ^[12] | 0 ^[13] | | |
| Units: Participants | | | | |

Notes:

[12] - Healthcare resource utilization data were not collected during the study.

[13] - Healthcare resource utilization data were not collected during the study.

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EuroQoL-5D (EQ-5D) Health Index Score

| | |
|-----------------|---|
| End point title | Change From Baseline in EuroQoL-5D (EQ-5D) Health Index Score ^[14] |
|-----------------|---|

End point description:

EQ-5D is a standardized, participant-rated questionnaire to assess health-related quality of life. The EQ-5D includes 2 components: the EQ-5D health state profile (descriptive system) and the EQ-5D visual analog scale (VAS). For the health state profile participants rate their perceived health state today on 5 dimensions: mobility, selfcare, usual activities, pain/discomfort, and anxiety/depression on a Likert-type scale from 1 to 3, where 1 = "no problems," 2 = "some problems," and 3 = "extreme problems." The EQ-5D Health Utility Index (HUI) was generated from the five health state domain scores, and ranges from -0.594 (worst) and 1 (best) imaginable health state, with -0.594 representing an "unconscious" health state.

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

End point timeframe:

Baseline and Days 85 and 169

Notes:

[14] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Endpoint was analyzed in the global study population only

| End point values | Pomalidomide 0.5 mg | Placebo | | |
|--------------------------------------|------------------------|-----------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 162 ^[15] | 82 ^[16] | | |
| Units: score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 85 | -0.0385 (± 0.2480) | -0.0298 (± 0.2129) | | |
| Day 169 | -0.0202 (± 0.1666) | 0.0766 (± 0.1546) | | |

Notes:

[15] - Day 85 N = 112

Day 169 N = 41

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in EuroQoL-5D (EQ-5D) Visual Analog Scale

| | |
|-----------------|--|
| End point title | Change From Baseline in EuroQoL-5D (EQ-5D) Visual Analog Scale ^[17] |
|-----------------|--|

End point description:

EQ-5D is a standardized, participant-rated questionnaire to assess health-related quality of life. The EQ-5D includes 2 components: the EQ-5D health state profile (descriptive system) and the EQ-5D visual analog scale (VAS). On the VAS the participant rates his/her health state on a line from 0 (worst imaginable health) to 100 (best imaginable health).

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

End point timeframe:

Baseline and Days 85 and 169

Notes:

[17] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Endpoint was analyzed in the global study population only

| End point values | Pomalidomide 0.5 mg | Placebo | | |
|--------------------------------------|------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 161 ^[18] | 81 ^[19] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 85 | 2.0 (± 20.78) | -1.4 (± 14.07) | | |
| Day 169 | 2.9 (± 22.85) | 0.3 (± 24.25) | | |

Notes:

[18] - Day 85 N = 111

Day 169 N = 41

[19] - Day 85 N = 55

Day 169 N = 13

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline in Functional Assessment of Cancer Therapy-Anemia (FACT-An) Total Score

| | |
|-----------------|--|
| End point title | Change From Baseline in Functional Assessment of Cancer Therapy-Anemia (FACT-An) Total Score ^[20] |
|-----------------|--|

End point description:

The FACT-An is a 47-item, cancer-specific questionnaire consisting of a core 27-item general questionnaire measuring the four general domains of QoL (physical, social/family, emotional and functional well-being), and an additional 20-item anemia questionnaire (FACT-An Anemia subscale) that measures 13 fatigue-associated items (FACT-F Fatigue subscale) and seven non-fatigue-related items. Each item is scored using a 5-point Likert rating scale (0 = Not at all; 1 = A little bit; 2 = Somewhat; 3 = Quite a bit; and 4 = Very much). FACT-An total score is calculated by adding all the FACT-An

subscales together. The total score ranges from 0-188 with higher scores representing better QOL.

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

End point timeframe:

Baseline and Days 85 and 169

Notes:

[20] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: Endpoint was analyzed in the global study population only

| End point values | Pomalidomide 0.5 mg | Placebo | | |
|--------------------------------------|------------------------|--------------------|--|--|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 159 ^[21] | 81 ^[22] | | |
| Units: units on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 85 | -2.1 (± 20.32) | 4.3 (± 18.73) | | |
| Day 169 | 6.2 (± 20.49) | 11.9 (± 18.60) | | |

Notes:

[21] - Day 85 N = 109

Day 169 N = 41

[22] - Day 85 N = 56

Day 169 N = 13

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Deaths are from first dose of study drug up to end of study, maximum time on-study was 85 months. AEs are from the first dose of study drug until 28 days after last dose; median treatment duration was 23.7, 23.9, and 24.0 weeks in each arm respectively.

Adverse event reporting additional description:

The safety population includes all participants who received at least one dose of study drug; one participant randomized to pomalidomide and one participant randomized to placebo in the global study did not receive treatment and are excluded from the safety population.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 15.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-----------------------------------|
| Reporting group title | Global Study: Pomalidomide 0.5 mg |
|-----------------------|-----------------------------------|

Reporting group description:

Participants received pomalidomide 0.5 mg/day by mouth for at least 168 days unless there were unacceptable side effects or disease progression. Participants who were RBC-transfusion independent or experienced clinical benefit could continue to receive pomalidomide until loss of RBC-transfusion independence response or clinical benefit, or other criteria for treatment discontinuation applied.

| | |
|-----------------------|-----------------------|
| Reporting group title | Global Study: Placebo |
|-----------------------|-----------------------|

Reporting group description:

Participants received placebo taken by mouth once daily for at least 168 days unless there were unacceptable side effects or disease progression. Participants who were RBC-transfusion independent or experienced clinical benefit could continue to receive placebo until loss of RBC-transfusion independence response or clinical benefit, or other criteria for treatment discontinuation applied.

| | |
|-----------------------|--------------------------------------|
| Reporting group title | China Extension: Pomalidomide 0.5 mg |
|-----------------------|--------------------------------------|

Reporting group description:

Participants received pomalidomide 0.5 mg/day by mouth for at least 168 days unless there were unacceptable side effects, disease progression, or they received a RBC-transfusion. Participants who experienced anemia response could continue treatment until the response was lost or other criteria for treatment discontinuation applied.

| Serious adverse events | Global Study: Pomalidomide 0.5 mg | Global Study: Placebo | China Extension: Pomalidomide 0.5 mg |
|---|---|--------------------------|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 76 / 167 (45.51%) | 29 / 83 (34.94%) | 0 / 15 (0.00%) |
| number of deaths (all causes) | 115 | 54 | 8 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| B-CELL LYMPHOMA | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| BASAL CELL CARCINOMA | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 167 (0.60%) | 1 / 83 (1.20%) | 0 / 15 (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 |
| HISTIOCYTOSIS HAEMATOPHAGIC | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| MALIGNANT MELANOMA | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| MYELOFIBROSIS | | | |
| subjects affected / exposed | 9 / 167 (5.39%) | 3 / 83 (3.61%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 9 | 3 / 5 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 3 | 1 / 3 | 0 / 0 |
| OESOPHAGEAL ADENOCARCINOMA | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| Vascular disorders | | | |
| AXILLARY VEIN THROMBOSIS | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| DEEP VEIN THROMBOSIS | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| HYPOTENSION | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| INTERMITTENT CLAUDICATION | | | |

| | | | |
|--|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| JUGULAR VEIN THROMBOSIS | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| PHLEBITIS | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| General disorders and administration site conditions | | | |
| ASTHENIA | | | |
| subjects affected / exposed | 2 / 167 (1.20%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| FATIGUE | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| GENERALISED OEDEMA | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| INFLUENZA LIKE ILLNESS | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| MULTI-ORGAN FAILURE | | | |
| subjects affected / exposed | 2 / 167 (1.20%) | 2 / 83 (2.41%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 1 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 1 / 2 | 0 / 0 |
| NON-CARDIAC CHEST PAIN | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| OEDEMA PERIPHERAL | | | |
| subjects affected / exposed | 4 / 167 (2.40%) | 0 / 83 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 1 / 4 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| PYREXIA | | | |
| subjects affected / exposed | 5 / 167 (2.99%) | 3 / 83 (3.61%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 2 / 5 | 0 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SUDDEN CARDIAC DEATH | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 83 (1.20%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| SUDDEN DEATH | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 83 (1.20%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| DYSPNOEA | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 1 / 83 (1.20%) | 0 / 15 (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 |
| EPISTAXIS | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| HYPOXIA | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| INTERSTITIAL LUNG DISEASE | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| PNEUMONITIS | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| PULMONARY EMBOLISM | | | |
| subjects affected / exposed | 2 / 167 (1.20%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| PULMONARY HYPERTENSION | | | |
| subjects affected / exposed | 2 / 167 (1.20%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| RESPIRATORY FAILURE | | | |
| subjects affected / exposed | 2 / 167 (1.20%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| Psychiatric disorders | | | |
| ABNORMAL BEHAVIOUR | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 83 (1.20%) | 0 / 15 (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 |
| Investigations | | | |
| ASPARTATE AMINOTRANSFERASE INCREASED | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 83 (1.20%) | 0 / 15 (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 |
| PLATELET COUNT INCREASED | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 83 (1.20%) | 0 / 15 (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 |

| | | | |
|---|-----------------|----------------|----------------|
| WHITE BLOOD CELL COUNT INCREASED | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 83 (1.20%) | 0 / 15 (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 |
| Injury, poisoning and procedural complications | | | |
| FALL | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 1 / 83 (1.20%) | 0 / 15 (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 |
| INJURY | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 / 167 (0.60%) | 1 / 83 (1.20%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 1 / 1 | 0 / 0 |
| SUBDURAL HAEMORRHAGE | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| TRANSFUSION-RELATED CIRCULATORY OVERLOAD | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 disorders | | | |
| ACUTE CORONARY SYNDROME | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 MYOCARDIAL INFARCTION | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| ATRIAL FIBRILLATION | | | |
| subjects affected / exposed | 2 / 167 (1.20%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| CARDIAC ARREST | | | |
| subjects affected / exposed | 2 / 167 (1.20%) | 0 / 83 (0.00%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| CARDIAC FAILURE | | | |
| subjects affected / exposed | 5 / 167 (2.99%) | 1 / 83 (1.20%) | 0 / 15 (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 |
| CARDIAC FAILURE ACUTE | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| CARDIAC FAILURE CONGESTIVE | | | |
| subjects affected / exposed | 3 / 167 (1.80%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| CONDUCTION DISORDER | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| CORONARY ARTERY DISEASE | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| Nervous system disorders | | | |
| CEREBROVASCULAR ACCIDENT | | | |

| | | | |
|---|------------------|----------------|----------------|
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 83 (1.20%) | 0 / 15 (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 |
| CONVULSION | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 83 (1.20%) | 0 / 15 (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 |
| LOSS OF CONSCIOUSNESS | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| SYNCOPE | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 83 (1.20%) | 0 / 15 (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 |
| VIITH NERVE PARALYSIS | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 83 (1.20%) | 0 / 15 (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 |
| Blood and lymphatic system disorders | | | |
| ANAEMIA | | | |
| subjects affected / exposed | 10 / 167 (5.99%) | 3 / 83 (3.61%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 3 / 14 | 1 / 3 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| DISSEMINATED INTRAVASCULAR COAGULATION | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 | 3 / 167 (1.80%) | 1 / 83 (1.20%) | 0 / 15 (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 |
| HAEMOLYSIS | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| HAEMOLYTIC ANAEMIA | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| NEUTROPENIA | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 1 / 83 (1.20%) | 0 / 15 (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 |
| PANCYTOPENIA | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| SPLENIC EMBOLISM | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| SPLENIC INFARCTION | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 1 / 83 (1.20%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 1 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| SPLENOMEGALY | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| THROMBOCYTOPENIA | | | |
| subjects affected / exposed | 3 / 167 (1.80%) | 2 / 83 (2.41%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 1 / 3 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastrointestinal disorders | | | |
| ABDOMINAL DISTENSION | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| ASCITES | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 | 0 / 167 (0.00%) | 2 / 83 (2.41%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 1 / 2 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| ENTEROCOLITIS | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| GASTRIC HAEMORRHAGE | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 83 (1.20%) | 0 / 15 (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 | 2 / 167 (1.20%) | 1 / 83 (1.20%) | 0 / 15 (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 |
| HAEMORRHOIDAL HAEMORRHAGE | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| HAEMORRHOIDS | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| MELAENA | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 | 0 / 167 (0.00%) | 1 / 83 (1.20%) | 0 / 15 (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 |
| Hepatobiliary disorders | | | |
| CHOLECYSTITIS | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 1 / 83 (1.20%) | 0 / 15 (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 |
| Skin and subcutaneous tissue disorders | | | |
| ACUTE FEBRILE NEUTROPHILIC DERMATOSIS | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| DRUG ERUPTION | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| LEUKOCYTOCLASTIC VASCULITIS | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| PETECHIAE | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 83 (1.20%) | 0 / 15 (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 |
| RASH MACULO-PAPULAR | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 ULCER | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 | | | |
| CALCULUS BLADDER | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 83 (1.20%) | 0 / 15 (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 |
| CALCULUS URETERIC | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| NEPHROLITHIASIS | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 83 (1.20%) | 0 / 15 (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 |
| NEPHROTIC SYNDROME | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 COLIC | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 FAILURE | | | |
| subjects affected / exposed | 3 / 167 (1.80%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| RENAL FAILURE ACUTE | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 1 / 83 (1.20%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| RENAL FAILURE CHRONIC | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| URINARY RETENTION | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 83 (1.20%) | 0 / 15 (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 |
| URINARY TRACT OBSTRUCTION | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| Musculoskeletal and connective tissue disorders | | | |
| BACK PAIN | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 83 (1.20%) | 0 / 15 (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 |
| Infections and infestations | | | |
| ATYPICAL PNEUMONIA | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| BACTEROIDES BACTERAEamia | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 83 (1.20%) | 0 / 15 (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 |
| BRONCHITIS | | | |
| subjects affected / exposed | 2 / 167 (1.20%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| BRONCHOPULMONARY ASPERGILLOSIS | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |

| | | | |
|---|-----------------|----------------|----------------|
| CELLULITIS | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| DEVICE RELATED INFECTION | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| ENTEROCOLITIS INFECTIOUS | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 CANDIDIASIS | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| INFECTIOUS PLEURAL EFFUSION | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| LUNG INFECTION | | | |
| subjects affected / exposed | 3 / 167 (1.80%) | 1 / 83 (1.20%) | 0 / 15 (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 |
| LYMPHADENITIS BACTERIAL | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 FASCIITIS | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| PARONYCHIA | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 83 (1.20%) | 0 / 15 (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 |
| PNEUMOCYSTIS JIROVECI PNEUMONIA | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 | | | |
| subjects affected / exposed | 6 / 167 (3.59%) | 4 / 83 (4.82%) | 0 / 15 (0.00%) |
| occurrences causally related to treatment / all | 0 / 7 | 0 / 4 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 0 |
| SEPSIS | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 1 / 83 (1.20%) | 0 / 15 (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 |
| SEPTIC SHOCK | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| SIALOADENITIS | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| STAPHYLOCOCCAL SEPSIS | | | |
| subjects affected / exposed | 2 / 167 (1.20%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| URINARY TRACT INFECTION | | | |

| | | | |
|---|-----------------|----------------|----------------|
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| UROSEPSIS | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| WOUND INFECTION | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| Metabolism and nutrition disorders | | | |
| DECREASED APPETITE | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |
| DEHYDRATION | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 83 (1.20%) | 0 / 15 (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 |
| DIABETIC KETOACIDOSIS | | | |
| subjects affected / exposed | 0 / 167 (0.00%) | 1 / 83 (1.20%) | 0 / 15 (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 |
| HYPOGLYCAEMIA | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 0 / 15 (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 |

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

| Non-serious adverse events | Global Study: Pomalidomide 0.5 mg | Global Study: Placebo | China Extension: Pomalidomide 0.5 mg |
|---|--|----------------------------------|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 155 / 167 (92.81%) | 76 / 83 (91.57%) | 12 / 15 (80.00%) |
| General disorders and administration site conditions | | | |
| ASTHENIA | | | |
| subjects affected / exposed | 23 / 167 (13.77%) | 8 / 83 (9.64%) | 0 / 15 (0.00%) |
| occurrences (all) | 31 | 9 | 0 |
| FATIGUE | | | |
| subjects affected / exposed | 35 / 167 (20.96%) | 17 / 83 (20.48%) | 3 / 15 (20.00%) |
| occurrences (all) | 51 | 23 | 4 |
| OEDEMA PERIPHERAL | | | |
| subjects affected / exposed | 53 / 167 (31.74%) | 14 / 83 (16.87%) | 1 / 15 (6.67%) |
| occurrences (all) | 83 | 18 | 1 |
| PYREXIA | | | |
| subjects affected / exposed | 30 / 167 (17.96%) | 9 / 83 (10.84%) | 2 / 15 (13.33%) |
| occurrences (all) | 51 | 13 | 2 |
| CHEST PAIN | | | |
| subjects affected / exposed | 2 / 167 (1.20%) | 0 / 83 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 2 | 0 | 2 |
| OEDEMA | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 1 | 0 | 1 |
| Respiratory, thoracic and mediastinal disorders | | | |
| COUGH | | | |
| subjects affected / exposed | 24 / 167 (14.37%) | 9 / 83 (10.84%) | 1 / 15 (6.67%) |
| occurrences (all) | 31 | 10 | 1 |
| DYSPNOEA | | | |
| subjects affected / exposed | 28 / 167 (16.77%) | 8 / 83 (9.64%) | 1 / 15 (6.67%) |
| occurrences (all) | 44 | 8 | 1 |
| DYSPNOEA EXERTIONAL | | | |
| subjects affected / exposed | 10 / 167 (5.99%) | 3 / 83 (3.61%) | 0 / 15 (0.00%) |
| occurrences (all) | 12 | 5 | 0 |
| EPISTAXIS | | | |
| subjects affected / exposed | 8 / 167 (4.79%) | 5 / 83 (6.02%) | 0 / 15 (0.00%) |
| occurrences (all) | 15 | 10 | 0 |

| | | | |
|--|-------------------------|------------------------|----------------------|
| PLEURAL EFFUSION subjects affected / exposed occurrences (all) | 5 / 167 (2.99%) 5 | 2 / 83 (2.41%) 2 | 1 / 15 (6.67%) 1 |
| Investigations WEIGHT DECREASED subjects affected / exposed occurrences (all) | 11 / 167 (6.59%) 12 | 3 / 83 (3.61%) 3 | 1 / 15 (6.67%) 1 |
| WHITE BLOOD CELL COUNT DECREASED subjects affected / exposed occurrences (all) | 2 / 167 (1.20%) 5 | 0 / 83 (0.00%) 0 | 1 / 15 (6.67%) 2 |
| WHITE BLOOD CELL COUNT INCREASED subjects affected / exposed occurrences (all) | 0 / 167 (0.00%) 0 | 1 / 83 (1.20%) 1 | 1 / 15 (6.67%) 2 |
| Injury, poisoning and procedural complications FALL subjects affected / exposed occurrences (all) | 7 / 167 (4.19%) 9 | 5 / 83 (6.02%) 7 | 0 / 15 (0.00%) 0 |
| LIGAMENT SPRAIN subjects affected / exposed occurrences (all) | 1 / 167 (0.60%) 1 | 0 / 83 (0.00%) 0 | 1 / 15 (6.67%) 1 |
| Cardiac disorders ARRHYTHMIA subjects affected / exposed occurrences (all) | 2 / 167 (1.20%) 4 | 1 / 83 (1.20%) 1 | 1 / 15 (6.67%) 1 |
| Nervous system disorders DIZZINESS subjects affected / exposed occurrences (all) | 17 / 167 (10.18%) 25 | 12 / 83 (14.46%) 16 | 0 / 15 (0.00%) 0 |
| SOMNOLENCE subjects affected / exposed occurrences (all) | 5 / 167 (2.99%) 5 | 5 / 83 (6.02%) 7 | 0 / 15 (0.00%) 0 |
| Blood and lymphatic system disorders ANAEMIA subjects affected / exposed occurrences (all) | 12 / 167 (7.19%) 16 | 5 / 83 (6.02%) 9 | 2 / 15 (13.33%) 2 |
| NEUTROPENIA | | | |

| | | | |
|--|-------------------|------------------|-----------------|
| subjects affected / exposed | 25 / 167 (14.97%) | 4 / 83 (4.82%) | 0 / 15 (0.00%) |
| occurrences (all) | 73 | 9 | 0 |
| THROMBOCYTOPENIA | | | |
| subjects affected / exposed | 21 / 167 (12.57%) | 12 / 83 (14.46%) | 1 / 15 (6.67%) |
| occurrences (all) | 41 | 22 | 1 |
| Gastrointestinal disorders | | | |
| ABDOMINAL DISTENSION | | | |
| subjects affected / exposed | 11 / 167 (6.59%) | 1 / 83 (1.20%) | 0 / 15 (0.00%) |
| occurrences (all) | 12 | 1 | 0 |
| ABDOMINAL PAIN | | | |
| subjects affected / exposed | 22 / 167 (13.17%) | 11 / 83 (13.25%) | 0 / 15 (0.00%) |
| occurrences (all) | 27 | 11 | 0 |
| ABDOMINAL PAIN UPPER | | | |
| subjects affected / exposed | 10 / 167 (5.99%) | 3 / 83 (3.61%) | 0 / 15 (0.00%) |
| occurrences (all) | 12 | 3 | 0 |
| CONSTIPATION | | | |
| subjects affected / exposed | 24 / 167 (14.37%) | 9 / 83 (10.84%) | 0 / 15 (0.00%) |
| occurrences (all) | 28 | 9 | 0 |
| DIARRHOEA | | | |
| subjects affected / exposed | 35 / 167 (20.96%) | 17 / 83 (20.48%) | 2 / 15 (13.33%) |
| occurrences (all) | 53 | 20 | 3 |
| NAUSEA | | | |
| subjects affected / exposed | 21 / 167 (12.57%) | 16 / 83 (19.28%) | 0 / 15 (0.00%) |
| occurrences (all) | 25 | 17 | 0 |
| VOMITING | | | |
| subjects affected / exposed | 12 / 167 (7.19%) | 7 / 83 (8.43%) | 0 / 15 (0.00%) |
| occurrences (all) | 18 | 9 | 0 |
| Hepatobiliary disorders | | | |
| HEPATIC CYST | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 1 | 0 | 1 |
| HEPATIC FUNCTION ABNORMAL | | | |
| subjects affected / exposed | 1 / 167 (0.60%) | 0 / 83 (0.00%) | 1 / 15 (6.67%) |
| occurrences (all) | 2 | 0 | 1 |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|------------------------|----------------------|----------------------|
| NIGHT SWEATS subjects affected / exposed occurrences (all) | 10 / 167 (5.99%) 12 | 3 / 83 (3.61%) 3 | 0 / 15 (0.00%) 0 |
| PRURITUS subjects affected / exposed occurrences (all) | 12 / 167 (7.19%) 14 | 5 / 83 (6.02%) 6 | 0 / 15 (0.00%) 0 |
| RASH subjects affected / exposed occurrences (all) | 11 / 167 (6.59%) 19 | 2 / 83 (2.41%) 2 | 0 / 15 (0.00%) 0 |
| Renal and urinary disorders CALCULUS URETERIC subjects affected / exposed occurrences (all) | 1 / 167 (0.60%) 2 | 0 / 83 (0.00%) 0 | 1 / 15 (6.67%) 1 |
| NEPHROLITHIASIS subjects affected / exposed occurrences (all) | 3 / 167 (1.80%) 4 | 0 / 83 (0.00%) 0 | 1 / 15 (6.67%) 1 |
| Musculoskeletal and connective tissue disorders ARTHRALGIA subjects affected / exposed occurrences (all) | 6 / 167 (3.59%) 9 | 8 / 83 (9.64%) 10 | 0 / 15 (0.00%) 0 |
| MUSCLE SPASMS subjects affected / exposed occurrences (all) | 9 / 167 (5.39%) 12 | 5 / 83 (6.02%) 6 | 0 / 15 (0.00%) 0 |
| PAIN IN EXTREMITY subjects affected / exposed occurrences (all) | 11 / 167 (6.59%) 13 | 6 / 83 (7.23%) 9 | 0 / 15 (0.00%) 0 |
| Infections and infestations BRONCHITIS subjects affected / exposed occurrences (all) | 9 / 167 (5.39%) 13 | 4 / 83 (4.82%) 5 | 2 / 15 (13.33%) 2 |
| NASOPHARYNGITIS subjects affected / exposed occurrences (all) | 13 / 167 (7.78%) 22 | 0 / 83 (0.00%) 0 | 0 / 15 (0.00%) 0 |
| PNEUMONIA subjects affected / exposed occurrences (all) | 10 / 167 (5.99%) 10 | 2 / 83 (2.41%) 2 | 1 / 15 (6.67%) 1 |

| | | | |
|------------------------------------|-------------------|----------------|----------------|
| UPPER RESPIRATORY TRACT INFECTION | | | |
| subjects affected / exposed | 10 / 167 (5.99%) | 5 / 83 (6.02%) | 1 / 15 (6.67%) |
| occurrences (all) | 11 | 5 | 2 |
| URINARY TRACT INFECTION | | | |
| subjects affected / exposed | 12 / 167 (7.19%) | 2 / 83 (2.41%) | 0 / 15 (0.00%) |
| occurrences (all) | 15 | 3 | 0 |
| Metabolism and nutrition disorders | | | |
| DECREASED APPETITE | | | |
| subjects affected / exposed | 20 / 167 (11.98%) | 7 / 83 (8.43%) | 0 / 15 (0.00%) |
| occurrences (all) | 22 | 7 | 0 |
| HYPERURICAEMIA | | | |
| subjects affected / exposed | 7 / 167 (4.19%) | 5 / 83 (6.02%) | 0 / 15 (0.00%) |
| occurrences (all) | 8 | 5 | 0 |
| HYPERGLYCAEMIA | | | |
| subjects affected / exposed | 3 / 167 (1.80%) | 2 / 83 (2.41%) | 1 / 15 (6.67%) |
| occurrences (all) | 3 | 2 | 1 |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|--|
| 28 September 2010 | Significant changes included: - The concept of Clinical Benefit was introduced to enable subjects with a 50% decrease in RBC-transfusion frequency to continue receiving study-medication even if RBC-transfusion independence was not achieved. This applied to subjects achieving RBC-transfusion independence if RBC transfusion independence ended due to an unrelated event. - Blood sampling was done in a subset of subjects to explore the pharmacokinetics of pomalidomide in this population. - RBC transfusions used to determine eligibility required a pre RBC-transfusion hemoglobin level ≤ 90 g/L. In subjects where a hemoglobin level < 90 g/L is dangerous, entry into the study with pre RBC-transfusion hemoglobin level > 90 g/L was allowed as long as a 6-month RBC-transfusion history was available to confirm eligibility. - If a subject could not be randomized within 28 days of signing Informed Consent due to logistical reasons, the medical monitor could approve randomization as soon as possible thereafter to eliminate the need to repeat screening procedures when not otherwise necessary. - A hemoglobin level measured > 72 hours before a RBC-transfusion could be used to determine eligibility if there were no intervening RBC-transfusions. - The medical monitor could approve the inclusion of a subject based on a bone marrow biopsy done > 6 months pre-screening. - In North America and the European Union a unit of RBC is approximately 240 mL and the average weight of a 50-year-old male is 90 kg. The protocol definition of ≥ 2 U RBC/28 days is equivalent to 5 mL/kg/28 days. In Japan and China a unit of RBCs is about 125 mL and the average weight of a 50-year-old male is 60 kg. The equivalent RBC-transfusion dose is 2.5 U/28 days. - Subjects receiving anti-coagulants other than low-dose aspirin were not excluded - Criteria for determination of blastic transformation based on blasts in blood was clarified. - 5-year follow-up for collection of new cancers was added |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported