



Clinical trial results:

A Prospective, Phase IV, Open-Label, Multi-Center Study Evaluating Changes in Bone Marrow Morphology in Adult Subjects Receiving Romiplostim for the Treatment of Thrombocytopenia Associated with Immune (Idiopathic) Thrombocytopenia Purpura (ITP)

Summary

| | |
|--------------------------|--|
| EudraCT number | 2008-004347-10 |
| Trial protocol | AT CZ DE PL BE ES HU SE EE IT LT SI BG |
| Global end of trial date | 09 January 2014 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 20 June 2016 |
| First version publication date | 30 July 2015 |

Trial information

Trial identification

| | |
|-----------------------|----------|
| Sponsor protocol code | 20080009 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT00907478 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|-----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 09 January 2014 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 09 January 2014 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the incidence of collagen fibrosis as evidenced by trichrome staining at Year 1, Year 2, or Year 3 after initial exposure of romiplostim.

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations and guidelines, and Food and Drug Administration (FDA) regulations. All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures.

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

Background therapy: -

Evidence for comparator: -

| | |
|---|----------------|
| Actual start date of recruitment | 11 August 2009 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Poland: 29 |
| Country: Number of subjects enrolled | Slovenia: 3 |
| Country: Number of subjects enrolled | Spain: 6 |
| Country: Number of subjects enrolled | Sweden: 5 |
| Country: Number of subjects enrolled | Austria: 4 |
| Country: Number of subjects enrolled | Belgium: 5 |
| Country: Number of subjects enrolled | Czech Republic: 12 |
| Country: Number of subjects enrolled | Estonia: 3 |
| Country: Number of subjects enrolled | Germany: 4 |
| Country: Number of subjects enrolled | Hungary: 7 |
| Country: Number of subjects enrolled | Italy: 6 |
| Country: Number of subjects enrolled | Lithuania: 11 |
| Country: Number of subjects enrolled | Australia: 16 |
| Country: Number of subjects enrolled | Canada: 12 |
| Country: Number of subjects enrolled | Mexico: 9 |
| Country: Number of subjects enrolled | Romania: 6 |
| Country: Number of subjects enrolled | Russian Federation: 15 |

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United States: 16 |
| Worldwide total number of subjects | 169 |
| EEA total number of subjects | 101 |

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) | 130 |
| From 65 to 84 years | 38 |
| 85 years and over | 1 |

Subject disposition

Recruitment

Recruitment details:

Eligible patients were adults diagnosed with immune (idiopathic) thrombocytopenic purpura (ITP) with a platelet count $< 50 \times 10^9/L$. The first patient enrolled 11 August 2009 and the last patient was enrolled 11 November 2010. Participants were enrolled at 60 study centers in Australia, Europe, and North America.

Pre-assignment

Screening details:

204 patients were screened, 35 were considered screen failures. Participants were enrolled sequentially into the following cohorts: • Bone marrow biopsy at Baseline and Year 1 • Bone marrow biopsy at Baseline and Year 2 • Bone marrow biopsy at Baseline and Year 3.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall Study (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|----------|
| Are arms mutually exclusive? | Yes |
| Arm title | Cohort 1 |

Arm description:

Participants received once weekly romiplostim for 3 years and had a bone marrow biopsy at Baseline and Year 1.

| | |
|--|-----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | romiplostim |
| Investigational medicinal product code | AMG 531 |
| Other name | Nplate |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Romiplostim administered by subcutaneous injection. The starting dose was 1 $\mu g/kg$; weekly dose increases continued in increments of 1 $\mu g/kg/week$ to a maximum dose of 10 $\mu g/kg$ in an attempt to reach a target platelet count of $\geq 50 \times 10^9/L$.

| | |
|------------------|----------|
| Arm title | Cohort 2 |
|------------------|----------|

Arm description:

Participants received once weekly romiplostim for 3 years and had a bone marrow biopsy at Baseline and Year 2.

| | |
|--|-----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | romiplostim |
| Investigational medicinal product code | AMG 531 |
| Other name | Nplate |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Romiplostim administered by subcutaneous injection. The starting dose was 1 $\mu g/kg$; weekly dose increases continued in increments of 1 $\mu g/kg/week$ to a maximum dose of 10 $\mu g/kg$ in an attempt to reach a target platelet count of $\geq 50 \times 10^9/L$.

| | |
|------------------|----------|
| Arm title | Cohort 3 |
|------------------|----------|

Arm description:

Participants received once weekly romiplostim for 3 years and had a bone marrow biopsy at Baseline and Year 3.

| | |
|--|-----------------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | romiplostim |
| Investigational medicinal product code | AMG 531 |
| Other name | Nplate |
| Pharmaceutical forms | Powder for solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Romiplostim administered by subcutaneous injection. The starting dose was 1 µg/kg; weekly dose increases continued in increments of 1 µg/kg/week to a maximum dose of 10 µg/kg in an attempt to reach a target platelet count of $\geq 50 \times 10^9/L$.

| Number of subjects in period 1 | Cohort 1 | Cohort 2 | Cohort 3 |
|---------------------------------------|----------|----------|----------|
| Started | 50 | 50 | 69 |
| Completed | 23 | 33 | 47 |
| Not completed | 27 | 17 | 22 |
| Consent withdrawn by subject | 8 | 9 | 6 |
| Physician decision | 2 | - | 3 |
| 'Ineligibility determined ' | - | - | 1 |
| Death | 4 | 2 | 1 |
| Other | 3 | - | 1 |
| Pregnancy | - | 1 | 1 |
| Adverse event | 3 | 1 | 2 |
| Lost to follow-up | 1 | - | - |
| Requirement for alternative therapy | 1 | 2 | 3 |
| Protocol-specified criteria | 5 | 2 | 3 |
| Noncompliance | - | - | 1 |

Baseline characteristics

Reporting groups

| | |
|--|----------|
| Reporting group title | Cohort 1 |
| Reporting group description: Participants received once weekly romiplostim for 3 years and had a bone marrow biopsy at Baseline and Year 1. | |
| Reporting group title | Cohort 2 |
| Reporting group description: Participants received once weekly romiplostim for 3 years and had a bone marrow biopsy at Baseline and Year 2. | |
| Reporting group title | Cohort 3 |
| Reporting group description: Participants received once weekly romiplostim for 3 years and had a bone marrow biopsy at Baseline and Year 3. | |

| Reporting group values | Cohort 1 | Cohort 2 | Cohort 3 |
|---|----------------|----------------|----------------|
| Number of subjects | 50 | 50 | 69 |
| Age categorical Units: Subjects | | | |
| Age continuous Units: years arithmetic mean standard deviation | 55.5 ± 17.1 | 48.6 ± 16.5 | 46.6 ± 16.3 |
| Gender categorical Units: Subjects | | | |
| Female | 27 | 38 | 49 |
| Male | 23 | 12 | 20 |
| Race/Ethnicity Units: Subjects | | | |
| White or Caucasian | 48 | 47 | 59 |
| Black or African American | 0 | 0 | 1 |
| Hispanic or Latino | 1 | 3 | 7 |
| Asian | 1 | 0 | 1 |
| Other | 0 | 0 | 1 |
| Number of Prior ITP Therapies Units: Subjects | | | |
| None | 0 | 0 | 0 |
| One | 16 | 16 | 29 |
| Two | 11 | 15 | 20 |
| Three | 8 | 9 | 10 |
| Four or more | 15 | 10 | 10 |
| Had Splenectomy Units: Subjects | | | |
| No | 28 | 35 | 46 |
| Yes | 22 | 15 | 23 |
| Any Prior History of Bone Marrow Abnormalities Units: Subjects | | | |

| | | | |
|-----|----|----|----|
| No | 48 | 47 | 64 |
| Yes | 2 | 3 | 5 |

| | | | |
|---|-----------------|-----------------|----------------|
| Time Since ITP Diagnosis Units: years arithmetic mean standard deviation | 9.94 ± 10.29 | 10.5 ± 11.87 | 5.36 ± 6.41 |
|---|-----------------|-----------------|----------------|

| | | | |
|------------------------------------|-------|--|--|
| Reporting group values | Total | | |
| Number of subjects | 169 | | |
| Age categorical Units: Subjects | | | |

| | | | |
|---|-----|--|--|
| Age continuous Units: years arithmetic mean standard deviation | - | | |
| Gender categorical Units: Subjects | | | |
| Female | 114 | | |
| Male | 55 | | |
| Race/Ethnicity Units: Subjects | | | |
| White or Caucasian | 154 | | |
| Black or African American | 1 | | |
| Hispanic or Latino | 11 | | |
| Asian | 2 | | |
| Other | 1 | | |
| Number of Prior ITP Therapies Units: Subjects | | | |
| None | 0 | | |
| One | 61 | | |
| Two | 46 | | |
| Three | 27 | | |
| Four or more | 35 | | |
| Had Splenectomy Units: Subjects | | | |
| No | 109 | | |
| Yes | 60 | | |
| Any Prior History of Bone Marrow Abnormalities Units: Subjects | | | |
| No | 159 | | |
| Yes | 10 | | |
| Time Since ITP Diagnosis Units: years arithmetic mean standard deviation | - | | |

End points

End points reporting groups

| | |
|--|-----------------|
| Reporting group title | Cohort 1 |
| Reporting group description: Participants received once weekly romiplostim for 3 years and had a bone marrow biopsy at Baseline and Year 1. | |
| Reporting group title | Cohort 2 |
| Reporting group description: Participants received once weekly romiplostim for 3 years and had a bone marrow biopsy at Baseline and Year 2. | |
| Reporting group title | Cohort 3 |
| Reporting group description: Participants received once weekly romiplostim for 3 years and had a bone marrow biopsy at Baseline and Year 3. | |
| Subject analysis set title | Overall |
| Subject analysis set type | Safety analysis |
| Subject analysis set description: Participants received once weekly romiplostim for 3 years. | |

Primary: Percentage of Subjects With Collagen Fibrosis

| | |
|--|--|
| End point title | Percentage of Subjects With Collagen Fibrosis ^[1] |
| End point description: The percentage of subjects who developed collagen fibrosis as evidenced by trichrome staining. Bone marrow biopsy samples were assessed using the modified Bauermeister grading scale by a central laboratory. | |
| End point type | Primary |
| End point timeframe: At Years 1, 2 or 3 after initial exposure of romiplostim | |
| 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: No formal hypothesis testing were performed on any endpoints in this open label study. | |

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | |
|----------------------------------|-------------------|-------------------|-------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 35 ^[2] | 39 ^[3] | 58 ^[4] | |
| Units: percentage of subject | | | | |
| number (confidence interval 95%) | 0 (0 to 10) | 0 (0 to 9) | 3.4 (0.4 to 11.9) | |

Notes:

[2] - Subjects with evaluable trichrome stain results

[3] - Subjects with evaluable trichrome stain results

[4] - Subjects with evaluable trichrome stain results

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Collagen Fibrosis 12 Weeks After Romiplostim Discontinuation in Subjects Who Developed Collagen Fibrosis at Years 1, 2, or 3

| | |
|-----------------|--|
| End point title | Number of Subjects With Collagen Fibrosis 12 Weeks After Romiplostim Discontinuation in Subjects Who Developed |
|-----------------|--|

End point description:

The number of subjects with collagen fibrosis as evidenced by trichrome staining 12 weeks after romiplostim discontinuation in subjects who developed collagen fibrosis at Years 1, 2, or 3 after initial exposure of romiplostim, assessed by the central laboratory using the modified Bauermeister grading scale.

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

End point timeframe:

12 weeks after romiplostim discontinuation

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | |
|-----------------------------|------------------|------------------|------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[5] | 0 ^[6] | 1 ^[7] | |
| Units: subjects | | | 0 | |

Notes:

[5] - Subjects with collagen fibrosis at Year 1

[6] - Subjects with collagen fibrosis at Year 2

[7] - Subjects with collagen fibrosis at Year 3 and with available trichrome staining results

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects Who Developed an Increased Modified Bauermeister Grade

| | |
|-----------------|---|
| End point title | Percentage of Subjects Who Developed an Increased Modified Bauermeister Grade |
|-----------------|---|

End point description:

Increased modified Bauermeister grade refers to an increase by ≥ 2 severity grades or an increase to grade 4 (ie, grade 0 to 2-4, grade 1 to 3-4, grade 2 to 4, or grade 3 to 4 over baseline). The modified Bauermeister scale provides a means of assessing the development of increased reticulin and collagen in bone marrow according to the following: Grade 0: No reticulin fibers demonstrable; Grade 1: Occasional fine individual fibers and foci of a fine fiber network; Grade 2: Fine fiber network throughout most of the section; no coarse fibers; Grade 3: Diffuse fiber network with scattered thick coarse fibers but no mature collagen (negative to trichrome staining); Grade 4: Diffuse, often coarse fiber network with areas of collagenization (positive trichrome staining).

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

End point timeframe:

At Year 1, Year 2, or Year 3 post romiplostim exposure

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | |
|----------------------------------|-------------------|-------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 34 ^[8] | 39 ^[9] | 58 ^[10] | |
| Units: percentage of subject | | | | |
| number (confidence interval 95%) | 0 (0 to 10.3) | 5.1 (0.6 to 17.3) | 12.1 (5 to 23.3) | |

Notes:

[8] - Subjects with evaluable reticulin silver stain results

[9] - Subjects with evaluable reticulin silver stain results

[10] - Subjects with evaluable reticulin silver stain results

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Clinically Relevant Changes in Total Cardiac Output Corrected (QTc) Intervals

| | |
|-----------------|---|
| End point title | Percentage of Subjects With Clinically Relevant Changes in Total Cardiac Output Corrected (QTc) Intervals |
|-----------------|---|

End point description:

A clinically relevant change in QTc (Fridericia) interval is defined as an absolute QTc interval >500 ms or a QTc Interval increase from Baseline >60 ms post romiplostim exposure. 12-lead electrocardiograms (ECG) were performed in triplicate at Baseline, Week 3 and Week 12; the average of the 3 values at each assessment was used.

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

End point timeframe:

Baseline, Week 3 and Week 12

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | |
|----------------------------------|--------------------|--------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 50 ^[11] | 50 ^[12] | 69 ^[13] | |
| Units: Percentage of subjects | | | | |
| number (confidence interval 95%) | 0 (0 to 7.1) | 0 (0 to 7.1) | 0 (0 to 5.2) | |

Notes:

[11] - All subjects who received at least one dose of romiplostim.

[12] - All subjects who received at least one dose of romiplostim.

[13] - All subjects who received at least one dose of romiplostim.

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Improvement of Reticulin to a Grade of ≤ 2 for Subjects Who Developed Grade 3 Reticulin

| | |
|-----------------|--|
| End point title | Number of Subjects With Improvement of Reticulin to a Grade of ≤ 2 for Subjects Who Developed Grade 3 Reticulin |
|-----------------|--|

End point description:

The number of subjects who had any improvement of reticulin to a grade of ≤ 2 for subjects who developed grade 3 reticulin after initial exposure to romiplostim as measured by the modified Bauermeister grading scale. The modified Bauermeister scale provides a means of assessing the development of increased reticulin and collagen in bone marrow according to the following: Grade 0: No reticulin fibers demonstrable; Grade 1: Occasional fine individual fibers and foci of a fine fiber network; Grade 2: Fine fiber network throughout most of the section; no coarse fibers; Grade 3: Diffuse fiber network with scattered thick coarse fibers but no mature collagen (negative to trichrome staining); Grade 4: Diffuse, often coarse fiber network with areas of collagenization (positive trichrome staining). Two subjects with grade 3 reticulin did not have a bone marrow biopsy performed 12 weeks after romiplostim discontinuation.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| 12 weeks after romiplostim discontinuation | |

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | |
|-----------------------------|-------------------|-------------------|-------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 0 ^[14] | 0 ^[15] | 3 ^[16] | |
| Units: subjects | | | 3 | |

Notes:

[14] - Subjects with Grade 3 reticulin at Year 1 and who had a follow-up bone marrow biopsy

[15] - Subjects with Grade 3 reticulin at Year 2 and who had a follow-up bone marrow biopsy

[16] - Subjects with Grade 3 reticulin at Year 3 and who had a follow-up bone marrow biopsy

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With CTCAE Grade ≥ 2 Shift in Anemia or Neutropenia

| | |
|-----------------|--|
| End point title | Percentage of Subjects With CTCAE Grade ≥ 2 Shift in Anemia or Neutropenia |
|-----------------|--|

End point description:

Anemia was identified by laboratory values with hemoglobin < the lower limit of normal (LLN) or the Medical Dictionary for Regulatory Activities (MedDRA) terms prespecified by the sponsor. Neutropenia was identified by laboratory values with absolute neutrophil count <1.8x10⁹/L or the MedDRA terms pre-specified by the sponsor. Severity was assessed using the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0, based on the following: Grade 1: Mild AE; Grade 2: Moderate AE; Grade 3: Severe AE; Grade 4: Life-threatening or disabling AE; Grade 5: Death related to AE.

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

End point timeframe:

From the first dose of study drug until 4 weeks after treatment discontinuation or 12 weeks after treatment discontinuation for patients who developed collagen fibrosis or a change to grade 3 reticulin; the overall median treatment duration was 154 weeks.

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | |
|-------------------------------------|--------------------|--------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 50 ^[17] | 50 ^[18] | 69 ^[19] | |
| Units: percentage of subjects | | | | |
| number (confidence interval 95%) | | | | |
| CTCAE grade ≥2 shift in anemia | 6 (1.3 to 16.5) | 4 (0.5 to 13.7) | 8.7 (3.3 to 18) | |
| CTCAE grade ≥2 shift in neutropenia | 8 (2.2 to 19.2) | 6 (1.3 to 16.5) | 13 (6.1 to 23.3) | |

Notes:

[17] - Subjects who received at least one dose of romiplostim

[18] - Subjects who received at least one dose of romiplostim

[19] - Subjects who received at least one dose of romiplostim

Statistical analyses

Secondary: Number of Subjects With Adverse Events (AEs)

| End point title | Number of Subjects With Adverse Events (AEs) |
|---|--|
| End point description: | |
| An AE was defined as any untoward medical occurrence in a participant that did not necessarily have a causal relationship with this treatment, or any such occurrence or worsening of a pre-existing medical condition from the first dose of investigational product through the last study visit. A serious adverse event is defined as an AE that is fatal or life threatening, requires or prolongs hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or other significant medical hazard. The relationship of each AE to the study drug was assessed by the investigator. The severity of each AE was graded using CTCAE 3.0; For any AEs not listed in CTCAE, the Amgen Standard Severity Scoring System was used: 1: Mild- Aware of sign or symptom, but easily tolerated; 2 Moderate- Discomfort enough to cause interference with usual activity; 3: Severe- Incapacitating with inability to work or do usual activity; 4: Life-threatening; 5: Fatal. | |
| End point type | Secondary |
| End point timeframe: | |
| From the first dose of study drug until 4 weeks after treatment discontinuation or 12 weeks after treatment discontinuation for patients who developed collagen fibrosis or a change to grade 3 reticulin; the overall median treatment duration was 154 weeks. | |

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | |
|--|--------------------|--------------------|--------------------|--|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 50 ^[20] | 50 ^[21] | 69 ^[22] | |
| Units: subjects | | | | |
| All adverse events | 46 | 45 | 67 | |
| Grade ≥ 2 | 39 | 39 | 59 | |
| Grade ≥ 3 | 25 | 21 | 38 | |
| Grade ≥ 4 | 13 | 8 | 16 | |
| Serious adverse events | 16 | 12 | 28 | |
| Leading to discontinuation of study drug | 6 | 5 | 4 | |
| Leading to discontinuation from study | 6 | 2 | 3 | |
| Fatal adverse events | 4 | 2 | 1 | |
| Treatment-related adverse events | 14 | 22 | 24 | |
| Treatment-related grade ≥ 2 | 8 | 14 | 10 | |
| Treatment-related grade ≥ 3 | 2 | 7 | 3 | |
| Treatment-related grade ≥ 4 | 0 | 1 | 0 | |
| Treatment-related serious adverse events | 1 | 2 | 3 | |
| Treatment-related -> discontinuation of study drug | 1 | 1 | 2 | |
| Treatment-related -> discontinuation from study | 1 | 0 | 2 | |
| Treatment-related fatal adverse events | 0 | 0 | 0 | |

Notes:

[20] - Subjects who received at least one dose of romiplostim

[21] - Subjects who received at least one dose of romiplostim

[22] - Subjects who received at least one dose of romiplostim

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects Who Developed Antibodies or Neutralizing Antibodies to Romiplostim or to Endogenous Thrombopoietin

| | |
|-----------------|---|
| End point title | Number of Subjects Who Developed Antibodies or Neutralizing Antibodies to Romiplostim or to Endogenous Thrombopoietin |
|-----------------|---|

End point description:

Two validated assays were used to test for antibodies to romiplostim, the thrombopoietin-mimetic peptide component of romiplostim (TMP) and to endogenous thrombopoietin (TPO). The first was an immunoassay to confirm the presence of antibodies. The second was a cell-based bioassay to detect neutralizing or inhibitory effects in vitro. If a sample was positive in both assays, a participant was defined as positive for neutralizing antibodies.

Persistent antibodies were those positive at the last timepoint tested and transient are defined as positive post-dose but negative at the last time point tested.

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

End point timeframe:

Every 24 weeks and at the end of study visit (4 weeks or 12 weeks after study drug discontinuation).

| End point values | Overall | | | |
|--|----------------------|--|--|--|
| Subject group type | Subject analysis set | | | |
| Number of subjects analysed | 69 ^[23] | | | |
| Units: subjects | | | | |
| Antibodies to romiplostim | 7 | | | |
| Persistent antibodies to romiplostim | 4 | | | |
| Transient antibodies to romiplostim | 3 | | | |
| Antibodies to TMP | 4 | | | |
| Persistent antibodies to TMP | 1 | | | |
| Transient antibodies to TMP | 3 | | | |
| Antibodies to TPO | 6 | | | |
| Persistent antibodies to TPO | 2 | | | |
| Transient antibodies to TPO | 4 | | | |
| Neutralizing antibodies to romiplostim | 1 | | | |
| Neutralizing antibodies to TPO | 0 | | | |

Notes:

[23] - All subjects who received at least one dose of romiplostim

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

3 years

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 16.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------|
| Reporting group title | Cohort 1 |
|-----------------------|----------|

Reporting group description:

Participants received once weekly romiplostim for 3 years and had a bone marrow biopsy at Baseline and Year 1.

| | |
|-----------------------|----------|
| Reporting group title | Cohort 2 |
|-----------------------|----------|

Reporting group description:

Participants received once weekly romiplostim for 3 years and had a bone marrow biopsy at Baseline and Year 2.

| | |
|-----------------------|----------|
| Reporting group title | Cohort 3 |
|-----------------------|----------|

Reporting group description:

Participants received once weekly romiplostim for 3 years and had a bone marrow biopsy at Baseline and Year 3.

| | |
|-----------------------|---------|
| Reporting group title | Overall |
|-----------------------|---------|

Reporting group description:

Participants received once weekly romiplostim for 3 years.

| Serious adverse events | Cohort 1 | Cohort 2 | Cohort 3 |
|---|------------------|------------------|------------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 16 / 50 (32.00%) | 12 / 50 (24.00%) | 28 / 69 (40.58%) |
| number of deaths (all causes) | 4 | 2 | 1 |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Endometrial adenocarcinoma | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 50 (2.00%) | 0 / 69 (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 |
| Plasma cell myeloma | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Prostate cancer | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 0 / 69 (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 |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 0 / 69 (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 |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 2 / 69 (2.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhage | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral embolism | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombosis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| Surgical and medical procedures | | | |

| | | | |
|--|----------------|----------------|----------------|
| Knee operation | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Tooth extraction | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 0 / 69 (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 | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 0 / 69 (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 | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 0 / 69 (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 |
| Pyrexia | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Reproductive system and breast disorders | | | |
| Adenomyosis | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 0 / 69 (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 |
| Endometriosis | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 0 / 69 (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 |
| Haemorrhagic ovarian cyst | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 0 / 69 (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 |
| Menorrhagia | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 0 / 69 (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 |
| Metrorrhagia | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 0 / 69 (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 |
| Ovarian cyst | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 50 (2.00%) | 0 / 69 (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 |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Epistaxis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pleural effusion | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pulmonary embolism | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 2 / 50 (4.00%) | 0 / 69 (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 |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 0 / 69 (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 thrombosis | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 0 / 69 (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 failure | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Psychiatric disorders | | | |
| Completed suicide | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 50 (2.00%) | 0 / 69 (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 |
| Investigations | | | |
| Clostridium test positive | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 0 / 69 (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 |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 0 / 69 (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 | | | |
| Facial bones fracture | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| | | | |
|---|----------------|----------------|----------------|
| Femoral neck fracture | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 50 (2.00%) | 0 / 69 (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 |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 0 / 69 (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 | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Procedural haemorrhage | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Subdural haematoma | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 0 / 69 (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 |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 2 / 69 (2.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Atrial flutter | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorder | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 0 / 69 (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 | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Myocardial infarction | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nervous system disorders | | | |
| Carotid artery stenosis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cerebral haemorrhage | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 0 / 69 (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 / 50 (4.00%) | 0 / 50 (0.00%) | 0 / 69 (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 |
| Complicated migraine | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 50 (2.00%) | 0 / 69 (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 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Headache | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 50 (2.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Ischaemic stroke | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Sensory disturbance | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Spinal claudication | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Syncope | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 2 / 69 (2.90%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 3 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemolysis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Haemorrhagic diathesis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Idiopathic thrombocytopenic purpura | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 50 (2.00%) | 2 / 69 (2.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Neutropenia | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | 0 / 50 (0.00%) | 4 / 69 (5.80%) |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 0 | 0 / 8 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Eye disorders | | | |
| Cataract | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 0 / 69 (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 |
| Conjunctival haemorrhage | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Glaucoma | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 0 / 69 (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 |
| Hyphaema | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 0 / 69 (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 |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 50 (2.00%) | 0 / 69 (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 |
| Acute abdomen | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Diarrhoea | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 0 / 69 (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 |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gingival disorder | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 0 / 69 (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 | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nausea | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 0 / 69 (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 gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 2 / 69 (2.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cholecystitis acute | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Portal vein thrombosis | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 0 / 69 (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 | | | |
| Hyperhidrosis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Lichenoid keratosis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Skin disorder | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 50 (2.00%) | 0 / 69 (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 |
| Renal and urinary disorders | | | |
| Anuria | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 50 (2.00%) | 0 / 69 (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 urethral | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Renal failure acute | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 50 (2.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| Endocrine disorders | | | |

| | | | |
|---|----------------|----------------|----------------|
| Goitre | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 50 (2.00%) | 0 / 69 (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 |
| Exostosis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Osteoarthritis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 2 / 69 (2.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 0 / 69 (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 |
| Infections and infestations | | | |
| Abscess jaw | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 0 / 69 (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 |
| Endocarditis | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 0 / 69 (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 |

| | | | |
|---|----------------|----------------|----------------|
| Fungal sepsis | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 0 / 69 (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 |
| Lobar pneumonia | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 50 (2.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Peritonitis | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| 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 | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 2 / 69 (2.90%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 2 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Urinary tract infection | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | 1 / 50 (2.00%) | 0 / 69 (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 |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 0 / 69 (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 |
| Diabetes mellitus inadequate control | | | |

| | | | |
|---|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Hyperkalaemia | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 1 / 50 (2.00%) | 0 / 69 (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 |

| Serious adverse events | Overall | | |
|---|-------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 56 / 169 (33.14%) | | |
| number of deaths (all causes) | 7 | | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Endometrial adenocarcinoma | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Plasma cell myeloma | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Prostate cancer | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Deep vein thrombosis | | | |

| | | | |
|--|-----------------|--|--|
| subjects affected / exposed | 2 / 169 (1.18%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhage | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hypertension | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral embolism | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peripheral ischaemia | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombosis | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Surgical and medical procedures | | | |
| Knee operation | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tooth extraction | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| General disorders and administration site conditions | | | |

| | | | |
|---|-----------------|--|--|
| Asthenia | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fatigue | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pyrexia | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Adenomyosis | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endometriosis | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhagic ovarian cyst | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Menorrhagia | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metrorrhagia | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Ovarian cyst | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vaginal haemorrhage | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Dyspnoea | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Epistaxis | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pleural effusion | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary embolism | | | |
| subjects affected / exposed | 2 / 169 (1.18%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pulmonary haemorrhage | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Pulmonary thrombosis | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Respiratory failure | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Completed suicide | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Investigations | | | |
| Clostridium test positive | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Weight decreased | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Facial bones fracture | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Femoral neck fracture | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Femur fracture | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Subdural haematoma | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Cardiac disorders | | | |
| Atrial fibrillation | | | |
| subjects affected / exposed | 2 / 169 (1.18%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Atrial flutter | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac disorder | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cardiac failure | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Myocardial infarction | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |

| | | | | |
|---|-----------------|--|--|--|
| Carotid artery stenosis | | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Cerebral haemorrhage | | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 1 | | | |
| Cerebrovascular accident | | | | |
| subjects affected / exposed | 2 / 169 (1.18%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Complicated migraine | | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Dizziness | | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Headache | | | | |
| subjects affected / exposed | 2 / 169 (1.18%) | | | |
| occurrences causally related to treatment / all | 0 / 2 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Ischaemic stroke | | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Sensory disturbance | | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | | |
| occurrences causally related to treatment / all | 0 / 1 | | | |
| deaths causally related to treatment / all | 0 / 0 | | | |
| Spinal claudication | | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Syncope | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 3 / 169 (1.78%) | | |
| occurrences causally related to treatment / all | 0 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemolysis | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhagic diathesis | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Idiopathic thrombocytopenic purpura | | | |
| subjects affected / exposed | 3 / 169 (1.78%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutropenia | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 6 / 169 (3.55%) | | |
| occurrences causally related to treatment / all | 0 / 10 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Eye disorders | | | |

| | | | |
|---|-----------------|--|--|
| Cataract | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Conjunctival haemorrhage | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Glaucoma | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyphaema | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Acute abdomen | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diarrhoea | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gingival disorder | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Melaena | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nausea | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Rectal haemorrhage | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper gastrointestinal haemorrhage | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hepatobiliary disorders | | | |
| Cholecystitis | | | |
| subjects affected / exposed | 2 / 169 (1.18%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cholecystitis acute | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Portal vein thrombosis | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|-----------------|--|--|
| Hyperhidrosis | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lichenoid keratosis | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin disorder | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Anuria | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Calculus urethral | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal failure acute | | | |
| subjects affected / exposed | 2 / 169 (1.18%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Endocrine disorders | | | |
| Goitre | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Back pain | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Exostosis | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 1 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Osteoarthritis | | | |
| subjects affected / exposed | 2 / 169 (1.18%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Abscess jaw | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cellulitis | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Endocarditis | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Fungal sepsis | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 1 | | |
| Lobar pneumonia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 2 / 169 (1.18%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 2 / 169 (1.18%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peritonitis | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 2 / 169 (1.18%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 3 / 169 (1.78%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metabolism and nutrition disorders | | | |
| Dehydration | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Diabetes mellitus inadequate control | | | |
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Hyperkalaemia | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 169 (0.59%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | Cohort 1 | Cohort 2 | Cohort 3 |
|---|------------------|------------------|------------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 45 / 50 (90.00%) | 43 / 50 (86.00%) | 66 / 69 (95.65%) |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | 3 / 50 (6.00%) | 10 / 69 (14.49%) |
| occurrences (all) | 2 | 7 | 23 |
| Hypertension | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 4 / 50 (8.00%) | 5 / 69 (7.25%) |
| occurrences (all) | 0 | 4 | 6 |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 0 / 50 (0.00%) | 8 / 69 (11.59%) |
| occurrences (all) | 1 | 0 | 10 |
| Fatigue | | | |
| subjects affected / exposed | 6 / 50 (12.00%) | 8 / 50 (16.00%) | 7 / 69 (10.14%) |
| occurrences (all) | 9 | 10 | 8 |
| Influenza like illness | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 3 / 50 (6.00%) | 3 / 69 (4.35%) |
| occurrences (all) | 0 | 7 | 5 |
| Local swelling | | | |
| subjects affected / exposed | 5 / 50 (10.00%) | 5 / 50 (10.00%) | 3 / 69 (4.35%) |
| occurrences (all) | 6 | 8 | 4 |
| Malaise | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 3 / 50 (6.00%) | 1 / 69 (1.45%) |
| occurrences (all) | 0 | 3 | 1 |
| Oedema peripheral | | | |
| subjects affected / exposed | 4 / 50 (8.00%) | 3 / 50 (6.00%) | 4 / 69 (5.80%) |
| occurrences (all) | 7 | 5 | 5 |
| Pain | | | |

| | | | |
|--|-----------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 2 / 50 (4.00%) 2 | 5 / 69 (7.25%) 5 |
| Pyrexia subjects affected / exposed occurrences (all) | 6 / 50 (12.00%) 7 | 4 / 50 (8.00%) 4 | 10 / 69 (14.49%) 19 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 4 / 50 (8.00%) 4 | 7 / 50 (14.00%) 8 | 13 / 69 (18.84%) 27 |
| Dyspnoea subjects affected / exposed occurrences (all) | 4 / 50 (8.00%) 5 | 0 / 50 (0.00%) 0 | 3 / 69 (4.35%) 3 |
| Epistaxis subjects affected / exposed occurrences (all) | 9 / 50 (18.00%) 9 | 10 / 50 (20.00%) 20 | 18 / 69 (26.09%) 38 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 1 | 6 / 50 (12.00%) 11 | 10 / 69 (14.49%) 14 |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 2 | 2 / 50 (4.00%) 3 | 5 / 69 (7.25%) 5 |
| Psychiatric disorders | | | |
| Insomnia subjects affected / exposed occurrences (all) | 3 / 50 (6.00%) 3 | 7 / 50 (14.00%) 9 | 3 / 69 (4.35%) 3 |
| Injury, poisoning and procedural complications | | | |
| Contusion subjects affected / exposed occurrences (all) | 6 / 50 (12.00%) 10 | 9 / 50 (18.00%) 16 | 19 / 69 (27.54%) 42 |
| Fall subjects affected / exposed occurrences (all) | 2 / 50 (4.00%) 2 | 2 / 50 (4.00%) 4 | 5 / 69 (7.25%) 5 |
| Laceration subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 1 | 3 / 50 (6.00%) 4 | 5 / 69 (7.25%) 8 |
| Procedural pain | | | |

| | | | |
|--|---------------------|---------------------|----------------------|
| subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 50 (0.00%) 0 | 7 / 69 (10.14%) 8 |
| Cardiac disorders | | | |
| Palpitations | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 1 / 50 (2.00%) | 4 / 69 (5.80%) |
| occurrences (all) | 1 | 1 | 5 |
| Tachycardia | | | |
| subjects affected / exposed | 3 / 50 (6.00%) | 0 / 50 (0.00%) | 1 / 69 (1.45%) |
| occurrences (all) | 3 | 0 | 1 |
| Nervous system disorders | | | |
| Dizziness | | | |
| subjects affected / exposed | 4 / 50 (8.00%) | 6 / 50 (12.00%) | 4 / 69 (5.80%) |
| occurrences (all) | 4 | 9 | 11 |
| Headache | | | |
| subjects affected / exposed | 12 / 50 (24.00%) | 14 / 50 (28.00%) | 25 / 69 (36.23%) |
| occurrences (all) | 17 | 39 | 62 |
| Paraesthesia | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 2 / 50 (4.00%) | 5 / 69 (7.25%) |
| occurrences (all) | 1 | 2 | 6 |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | 2 / 50 (4.00%) | 4 / 69 (5.80%) |
| occurrences (all) | 2 | 4 | 5 |
| Idiopathic thrombocytopenic purpura | | | |
| subjects affected / exposed | 8 / 50 (16.00%) | 6 / 50 (12.00%) | 8 / 69 (11.59%) |
| occurrences (all) | 27 | 13 | 23 |
| Iron deficiency anaemia | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | 1 / 50 (2.00%) | 4 / 69 (5.80%) |
| occurrences (all) | 2 | 1 | 4 |
| Neutrophilia | | | |
| subjects affected / exposed | 3 / 50 (6.00%) | 0 / 50 (0.00%) | 0 / 69 (0.00%) |
| occurrences (all) | 3 | 0 | 0 |
| Thrombocytopenia | | | |
| subjects affected / exposed | 8 / 50 (16.00%) | 3 / 50 (6.00%) | 6 / 69 (8.70%) |
| occurrences (all) | 21 | 4 | 15 |
| Ear and labyrinth disorders | | | |

| | | | |
|--|-----------------------|-----------------------|------------------------|
| Vertigo subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 2 | 1 / 50 (2.00%) 1 | 5 / 69 (7.25%) 7 |
| Eye disorders Cataract subjects affected / exposed occurrences (all) | 3 / 50 (6.00%) 3 | 2 / 50 (4.00%) 2 | 2 / 69 (2.90%) 2 |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) | 2 / 50 (4.00%) 2 | 2 / 50 (4.00%) 2 | 8 / 69 (11.59%) 12 |
| Abdominal pain lower subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 0 / 50 (0.00%) 0 | 4 / 69 (5.80%) 4 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 2 / 50 (4.00%) 2 | 3 / 50 (6.00%) 5 | 5 / 69 (7.25%) 6 |
| Constipation subjects affected / exposed occurrences (all) | 3 / 50 (6.00%) 3 | 3 / 50 (6.00%) 3 | 5 / 69 (7.25%) 7 |
| Diarrhoea subjects affected / exposed occurrences (all) | 7 / 50 (14.00%) 10 | 7 / 50 (14.00%) 14 | 18 / 69 (26.09%) 35 |
| Gingival bleeding subjects affected / exposed occurrences (all) | 3 / 50 (6.00%) 3 | 5 / 50 (10.00%) 11 | 13 / 69 (18.84%) 21 |
| Haemorrhoids subjects affected / exposed occurrences (all) | 0 / 50 (0.00%) 0 | 1 / 50 (2.00%) 3 | 4 / 69 (5.80%) 4 |
| Mouth haemorrhage subjects affected / exposed occurrences (all) | 6 / 50 (12.00%) 12 | 5 / 50 (10.00%) 8 | 2 / 69 (2.90%) 3 |
| Nausea subjects affected / exposed occurrences (all) | 6 / 50 (12.00%) 6 | 7 / 50 (14.00%) 10 | 11 / 69 (15.94%) 21 |
| Vomiting | | | |

| | | | |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed occurrences (all) | 5 / 50 (10.00%) 7 | 6 / 50 (12.00%) 7 | 8 / 69 (11.59%) 9 |
| Skin and subcutaneous tissue disorders | | | |
| Alopecia | | | |
| subjects affected / exposed | 0 / 50 (0.00%) | 0 / 50 (0.00%) | 7 / 69 (10.14%) |
| occurrences (all) | 0 | 0 | 8 |
| Ecchymosis | | | |
| subjects affected / exposed | 2 / 50 (4.00%) | 3 / 50 (6.00%) | 4 / 69 (5.80%) |
| occurrences (all) | 3 | 23 | 8 |
| Petechiae | | | |
| subjects affected / exposed | 9 / 50 (18.00%) | 11 / 50 (22.00%) | 14 / 69 (20.29%) |
| occurrences (all) | 22 | 14 | 27 |
| Pruritus | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 6 / 50 (12.00%) | 8 / 69 (11.59%) |
| occurrences (all) | 1 | 8 | 16 |
| Rash | | | |
| subjects affected / exposed | 3 / 50 (6.00%) | 4 / 50 (8.00%) | 7 / 69 (10.14%) |
| occurrences (all) | 3 | 4 | 12 |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 8 / 50 (16.00%) | 10 / 50 (20.00%) | 19 / 69 (27.54%) |
| occurrences (all) | 11 | 12 | 39 |
| Back pain | | | |
| subjects affected / exposed | 5 / 50 (10.00%) | 8 / 50 (16.00%) | 11 / 69 (15.94%) |
| occurrences (all) | 6 | 13 | 16 |
| Bone pain | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 4 / 50 (8.00%) | 1 / 69 (1.45%) |
| occurrences (all) | 1 | 4 | 1 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 2 / 50 (4.00%) | 5 / 69 (7.25%) |
| occurrences (all) | 1 | 3 | 6 |
| Myalgia | | | |
| subjects affected / exposed | 1 / 50 (2.00%) | 2 / 50 (4.00%) | 9 / 69 (13.04%) |
| occurrences (all) | 1 | 2 | 17 |
| Neck pain | | | |

| | | | |
|---|------------------------|------------------------|------------------------|
| subjects affected / exposed occurrences (all) | 2 / 50 (4.00%) 2 | 1 / 50 (2.00%) 1 | 4 / 69 (5.80%) 4 |
| Pain in extremity subjects affected / exposed occurrences (all) | 4 / 50 (8.00%) 11 | 5 / 50 (10.00%) 5 | 8 / 69 (11.59%) 14 |
| Infections and infestations | | | |
| Bronchitis subjects affected / exposed occurrences (all) | 3 / 50 (6.00%) 5 | 9 / 50 (18.00%) 10 | 12 / 69 (17.39%) 16 |
| Influenza subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 1 | 7 / 50 (14.00%) 16 | 8 / 69 (11.59%) 24 |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 6 / 50 (12.00%) 8 | 21 / 50 (42.00%) 41 | 14 / 69 (20.29%) 42 |
| Pharyngitis subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 1 | 4 / 50 (8.00%) 4 | 6 / 69 (8.70%) 24 |
| Respiratory tract infection subjects affected / exposed occurrences (all) | 2 / 50 (4.00%) 2 | 3 / 50 (6.00%) 4 | 2 / 69 (2.90%) 2 |
| Sinusitis subjects affected / exposed occurrences (all) | 3 / 50 (6.00%) 6 | 5 / 50 (10.00%) 17 | 7 / 69 (10.14%) 14 |
| Upper respiratory tract infection subjects affected / exposed occurrences (all) | 11 / 50 (22.00%) 25 | 7 / 50 (14.00%) 9 | 13 / 69 (18.84%) 31 |
| Urinary tract infection subjects affected / exposed occurrences (all) | 4 / 50 (8.00%) 4 | 6 / 50 (12.00%) 7 | 6 / 69 (8.70%) 11 |
| Viral infection subjects affected / exposed occurrences (all) | 1 / 50 (2.00%) 4 | 3 / 50 (6.00%) 3 | 7 / 69 (10.14%) 9 |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia | | | |

| | | | |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 2 / 50 (4.00%) | 3 / 50 (6.00%) | 2 / 69 (2.90%) |
| occurrences (all) | 2 | 4 | 2 |

| Non-serious adverse events | Overall | | |
|---|--------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 154 / 169 (91.12%) | | |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 15 / 169 (8.88%) | | |
| occurrences (all) | 32 | | |
| Hypertension | | | |
| subjects affected / exposed | 9 / 169 (5.33%) | | |
| occurrences (all) | 10 | | |
| General disorders and administration site conditions | | | |
| Chest pain | | | |
| subjects affected / exposed | 9 / 169 (5.33%) | | |
| occurrences (all) | 11 | | |
| Fatigue | | | |
| subjects affected / exposed | 21 / 169 (12.43%) | | |
| occurrences (all) | 27 | | |
| Influenza like illness | | | |
| subjects affected / exposed | 6 / 169 (3.55%) | | |
| occurrences (all) | 12 | | |
| Local swelling | | | |
| subjects affected / exposed | 13 / 169 (7.69%) | | |
| occurrences (all) | 18 | | |
| Malaise | | | |
| subjects affected / exposed | 4 / 169 (2.37%) | | |
| occurrences (all) | 4 | | |
| Oedema peripheral | | | |
| subjects affected / exposed | 11 / 169 (6.51%) | | |
| occurrences (all) | 17 | | |
| Pain | | | |
| subjects affected / exposed | 7 / 169 (4.14%) | | |
| occurrences (all) | 7 | | |
| Pyrexia | | | |

| | | | |
|--|-------------------------|--|--|
| subjects affected / exposed occurrences (all) | 20 / 169 (11.83%) 30 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough | | | |
| subjects affected / exposed | 24 / 169 (14.20%) | | |
| occurrences (all) | 39 | | |
| Dyspnoea | | | |
| subjects affected / exposed | 7 / 169 (4.14%) | | |
| occurrences (all) | 8 | | |
| Epistaxis | | | |
| subjects affected / exposed | 37 / 169 (21.89%) | | |
| occurrences (all) | 67 | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 17 / 169 (10.06%) | | |
| occurrences (all) | 26 | | |
| Rhinorrhoea | | | |
| subjects affected / exposed | 8 / 169 (4.73%) | | |
| occurrences (all) | 10 | | |
| Psychiatric disorders | | | |
| Insomnia | | | |
| subjects affected / exposed | 13 / 169 (7.69%) | | |
| occurrences (all) | 15 | | |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 34 / 169 (20.12%) | | |
| occurrences (all) | 68 | | |
| Fall | | | |
| subjects affected / exposed | 9 / 169 (5.33%) | | |
| occurrences (all) | 11 | | |
| Laceration | | | |
| subjects affected / exposed | 9 / 169 (5.33%) | | |
| occurrences (all) | 13 | | |
| Procedural pain | | | |
| subjects affected / exposed | 7 / 169 (4.14%) | | |
| occurrences (all) | 8 | | |
| Cardiac disorders | | | |

| | | | |
|---|---|--|--|
| Palpitations subjects affected / exposed occurrences (all) | 6 / 169 (3.55%) 7 | | |
| Tachycardia subjects affected / exposed occurrences (all) | 4 / 169 (2.37%) 4 | | |
| Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all) | 14 / 169 (8.28%) 24 51 / 169 (30.18%) 118 8 / 169 (4.73%) 9 | | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) Idiopathic thrombocytopenic purpura subjects affected / exposed occurrences (all) Iron deficiency anaemia subjects affected / exposed occurrences (all) Neutrophilia subjects affected / exposed occurrences (all) Thrombocytopenia subjects affected / exposed occurrences (all) | 8 / 169 (4.73%) 11 22 / 169 (13.02%) 63 7 / 169 (4.14%) 7 3 / 169 (1.78%) 3 17 / 169 (10.06%) 40 | | |
| Ear and labyrinth disorders Vertigo subjects affected / exposed occurrences (all) | 7 / 169 (4.14%) 10 | | |
| Eye disorders | | | |

| | | | |
|--|-------------------------|--|--|
| Cataract subjects affected / exposed occurrences (all) | 7 / 169 (4.14%) 7 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain subjects affected / exposed occurrences (all) | 12 / 169 (7.10%) 16 | | |
| Abdominal pain lower subjects affected / exposed occurrences (all) | 4 / 169 (2.37%) 4 | | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 10 / 169 (5.92%) 13 | | |
| Constipation subjects affected / exposed occurrences (all) | 11 / 169 (6.51%) 13 | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 32 / 169 (18.93%) 59 | | |
| Gingival bleeding subjects affected / exposed occurrences (all) | 21 / 169 (12.43%) 35 | | |
| Haemorrhoids subjects affected / exposed occurrences (all) | 5 / 169 (2.96%) 7 | | |
| Mouth haemorrhage subjects affected / exposed occurrences (all) | 13 / 169 (7.69%) 23 | | |
| Nausea subjects affected / exposed occurrences (all) | 24 / 169 (14.20%) 37 | | |
| Vomiting subjects affected / exposed occurrences (all) | 19 / 169 (11.24%) 23 | | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|-------------------|--|--|
| Alopecia | | | |
| subjects affected / exposed | 7 / 169 (4.14%) | | |
| occurrences (all) | 8 | | |
| Ecchymosis | | | |
| subjects affected / exposed | 9 / 169 (5.33%) | | |
| occurrences (all) | 34 | | |
| Petechiae | | | |
| subjects affected / exposed | 34 / 169 (20.12%) | | |
| occurrences (all) | 63 | | |
| Pruritus | | | |
| subjects affected / exposed | 15 / 169 (8.88%) | | |
| occurrences (all) | 25 | | |
| Rash | | | |
| subjects affected / exposed | 14 / 169 (8.28%) | | |
| occurrences (all) | 19 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 37 / 169 (21.89%) | | |
| occurrences (all) | 62 | | |
| Back pain | | | |
| subjects affected / exposed | 24 / 169 (14.20%) | | |
| occurrences (all) | 35 | | |
| Bone pain | | | |
| subjects affected / exposed | 6 / 169 (3.55%) | | |
| occurrences (all) | 6 | | |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 8 / 169 (4.73%) | | |
| occurrences (all) | 10 | | |
| Myalgia | | | |
| subjects affected / exposed | 12 / 169 (7.10%) | | |
| occurrences (all) | 20 | | |
| Neck pain | | | |
| subjects affected / exposed | 7 / 169 (4.14%) | | |
| occurrences (all) | 7 | | |
| Pain in extremity | | | |

| | | | |
|------------------------------------|-------------------|--|--|
| subjects affected / exposed | 17 / 169 (10.06%) | | |
| occurrences (all) | 30 | | |
| Infections and infestations | | | |
| Bronchitis | | | |
| subjects affected / exposed | 24 / 169 (14.20%) | | |
| occurrences (all) | 31 | | |
| Influenza | | | |
| subjects affected / exposed | 16 / 169 (9.47%) | | |
| occurrences (all) | 41 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 41 / 169 (24.26%) | | |
| occurrences (all) | 91 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 11 / 169 (6.51%) | | |
| occurrences (all) | 29 | | |
| Respiratory tract infection | | | |
| subjects affected / exposed | 7 / 169 (4.14%) | | |
| occurrences (all) | 8 | | |
| Sinusitis | | | |
| subjects affected / exposed | 15 / 169 (8.88%) | | |
| occurrences (all) | 37 | | |
| Upper respiratory tract infection | | | |
| subjects affected / exposed | 31 / 169 (18.34%) | | |
| occurrences (all) | 65 | | |
| Urinary tract infection | | | |
| subjects affected / exposed | 16 / 169 (9.47%) | | |
| occurrences (all) | 22 | | |
| Viral infection | | | |
| subjects affected / exposed | 11 / 169 (6.51%) | | |
| occurrences (all) | 16 | | |
| Metabolism and nutrition disorders | | | |
| Hypokalaemia | | | |
| subjects affected / exposed | 7 / 169 (4.14%) | | |
| occurrences (all) | 8 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|-------------------|---|
| 15 September 2010 | <ul style="list-style-type: none">- Added a request for the collection of bone marrow biopsies for subjects that early terminate and have not previously provided a cohort-defined biopsy.- Bone marrow aspirates will no longer be specifically requested per protocol as there are no planned evaluations or analysis for these samples. However, additional bone marrow biopsies and aspirates may be performed if clinically indicated at the discretion of the investigator and/or Amgen.- Clarified frequency of bone marrow panel review |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported