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 x 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 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 ≥ 50 x 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 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 ≥ 50 x 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 ≥ 50 x 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	55.5	48.6	46.6
standard deviation	± 17.1	± 16.5	± 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	9.94	10.5	5.36
standard deviation	± 10.29	± 11.87	± 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

	Collagen Fibrosis at Years 1, 2, or 3

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] - Sujects 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 trichome 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 course 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 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 course 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 romiploastim 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 <1.8x10^9/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

No statistical analyses for this end point

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

subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	7 / 69 (10.14%)
occurrences (all)	0	0	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	1 / 50 (2.00%)	1 / 50 (2.00%)	5 / 69 (7.25%)
occurrences (all)	2	1	7
Eye disorders			
Cataract			
subjects affected / exposed	3 / 50 (6.00%)	2 / 50 (4.00%)	2 / 69 (2.90%)
occurrences (all)	3	2	2
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 50 (4.00%)	2 / 50 (4.00%)	8 / 69 (11.59%)
occurrences (all)	2	2	12
Abdominal pain lower			
subjects affected / exposed	0 / 50 (0.00%)	0 / 50 (0.00%)	4 / 69 (5.80%)
occurrences (all)	0	0	4
Abdominal pain upper			
subjects affected / exposed	2 / 50 (4.00%)	3 / 50 (6.00%)	5 / 69 (7.25%)
occurrences (all)	2	5	6
Constipation			
subjects affected / exposed	3 / 50 (6.00%)	3 / 50 (6.00%)	5 / 69 (7.25%)
occurrences (all)	3	3	7
Diarrhoea			
subjects affected / exposed	7 / 50 (14.00%)	7 / 50 (14.00%)	18 / 69 (26.09%)
occurrences (all)	10	14	35
Gingival bleeding			
subjects affected / exposed	3 / 50 (6.00%)	5 / 50 (10.00%)	13 / 69 (18.84%)
occurrences (all)	3	11	21
Haemorrhoids			
subjects affected / exposed	0 / 50 (0.00%)	1 / 50 (2.00%)	4 / 69 (5.80%)
occurrences (all)	0	3	4
Mouth haemorrhage			
subjects affected / exposed	6 / 50 (12.00%)	5 / 50 (10.00%)	2 / 69 (2.90%)
occurrences (all)	12	8	3
Nausea			
subjects affected / exposed	6 / 50 (12.00%)	7 / 50 (14.00%)	11 / 69 (15.94%)
occurrences (all)	6	10	21
Vomiting			

subjects affected / exposed	5 / 50 (10.00%)	6 / 50 (12.00%)	8 / 69 (11.59%)
occurrences (all)	7	7	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	2 / 50 (4.00%)	1 / 50 (2.00%)	4 / 69 (5.80%)
occurrences (all)	2	1	4
Pain in extremity			
subjects affected / exposed	4 / 50 (8.00%)	5 / 50 (10.00%)	8 / 69 (11.59%)
occurrences (all)	11	5	14
Infections and infestations			
Bronchitis			
subjects affected / exposed	3 / 50 (6.00%)	9 / 50 (18.00%)	12 / 69 (17.39%)
occurrences (all)	5	10	16
Influenza			
subjects affected / exposed	1 / 50 (2.00%)	7 / 50 (14.00%)	8 / 69 (11.59%)
occurrences (all)	1	16	24
Nasopharyngitis			
subjects affected / exposed	6 / 50 (12.00%)	21 / 50 (42.00%)	14 / 69 (20.29%)
occurrences (all)	8	41	42
Pharyngitis			
subjects affected / exposed	1 / 50 (2.00%)	4 / 50 (8.00%)	6 / 69 (8.70%)
occurrences (all)	1	4	24
Respiratory tract infection			
subjects affected / exposed	2 / 50 (4.00%)	3 / 50 (6.00%)	2 / 69 (2.90%)
occurrences (all)	2	4	2
Sinusitis			
subjects affected / exposed	3 / 50 (6.00%)	5 / 50 (10.00%)	7 / 69 (10.14%)
occurrences (all)	6	17	14
Upper respiratory tract infection			
subjects affected / exposed	11 / 50 (22.00%)	7 / 50 (14.00%)	13 / 69 (18.84%)
occurrences (all)	25	9	31
Urinary tract infection			
subjects affected / exposed	4 / 50 (8.00%)	6 / 50 (12.00%)	6 / 69 (8.70%)
occurrences (all)	4	7	11
Viral infection			
subjects affected / exposed	1 / 50 (2.00%)	3 / 50 (6.00%)	7 / 69 (10.14%)
occurrences (all)	4	3	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	20 / 169 (11.83%)		
occurrences (all)	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) Tachycardia subjects affected / exposed occurrences (all)	 6 / 169 (3.55%) 7 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	7 / 169 (4.14%)		
occurrences (all)	7		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	12 / 169 (7.10%)		
occurrences (all)	16		
Abdominal pain lower			
subjects affected / exposed	4 / 169 (2.37%)		
occurrences (all)	4		
Abdominal pain upper			
subjects affected / exposed	10 / 169 (5.92%)		
occurrences (all)	13		
Constipation			
subjects affected / exposed	11 / 169 (6.51%)		
occurrences (all)	13		
Diarrhoea			
subjects affected / exposed	32 / 169 (18.93%)		
occurrences (all)	59		
Gingival bleeding			
subjects affected / exposed	21 / 169 (12.43%)		
occurrences (all)	35		
Haemorrhoids			
subjects affected / exposed	5 / 169 (2.96%)		
occurrences (all)	7		
Mouth haemorrhage			
subjects affected / exposed	13 / 169 (7.69%)		
occurrences (all)	23		
Nausea			
subjects affected / exposed	24 / 169 (14.20%)		
occurrences (all)	37		
Vomiting			
subjects affected / exposed	19 / 169 (11.24%)		
occurrences (all)	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	- 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