Clinical trial results:
An Open Label Study Evaluating the Safety and Efficacy of Long-Term Dosing of AMG 531 in Thrombocytopenic Subjects with Immune (Idiopathic) Thrombocytopenic Purpura (ITP)

Summary

EudraCT number	2004-000172-13
Trial protocol	GB DE BE AT CZ IT
Global end of trial date	26 January 2010

Results information

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	20030213

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00116688
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen, Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, 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)	
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 January 2010
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 January 2010
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to determine the safety of romiplostim as a long-term treatment in thrombocytopenic subjects with ITP, to evaluate the long-term platelet response to romiplostim, and to evaluate changes in patient reported outcomes due to the use of romiplostim. Participants must have previously completed a romiplostim ITP study.

Protection of trial subjects:

This study was conducted in accordance with the principles of the US Food and Drug Administration (FDA) and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations and guidelines.
Before any subject participated in the study, the investigator was to obtain written informed consent and/or assent for the pediatric population from the subject following adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. Informed consent was to be obtained before any protocol-specific screening procedures or administration of romiplostim.
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	02 August 2004
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	Australia: 17
Country: Number of subjects enrolled	Austria: 6
Country: Number of subjects enrolled	Belgium: 19
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Czech Republic: 1
Country: Number of subjects enrolled	France: 15
Country: Number of subjects enrolled	Germany: 20
Country: Number of subjects enrolled	Italy: 5
Country: Number of subjects enrolled	Netherlands: 12
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Spain: 7
Country: Number of subjects enrolled	United Kingdom: 6
Country: Number of subjects enrolled	United States: 200

Worldwide total number of subjects	313
EEA total number of subjects	92

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)	1
Children (2-11 years)	11
Adolescents (12-17 years)	9
Adults (18-64 years)	208
From 65 to 84 years	77
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled from 2 August 2004 through 15 April 2009

Pre-assignment

Screening details:

To be eligible for the study, subjects were required to have previously completed a romiplostim ITP study. The only current ITP treatments permitted were corticosteroids, azathioprine, and/or danazol administered at a constant dose and schedule.

Period 1

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

Arms

Arm title	Romiplostim

Arm description:

Romiplostim was administered to adult participants subcutaneously weekly at doses up to 30 µg/kg based on platelet counts. After Amendment 1 the maximum weekly dose was reduced to 15 µg/kg, and after Amendment 2 the maximum weekly dose was reduced to 10 µg/kg. However, participants enrolled prior to Amendment 2 who were receiving >10 µg/kg were permitted to remain on that higher dose, but could not increase their dose. In addition, if the participant's dose was decreased, it could not be increased to >10 µg/kg.
Romiplostim was administered to pediatric participants subcutaneously weekly at doses up to 10 µg/kg based on platelet counts.

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:

Administered by subcutaneous injection

Number of subjects in period 1	Romiplostim
Started	313
Received study medication	311
Completed	217
Not completed	96
Physician decision	7
Consent withdrawn by subject	28
Other	11
'Death '	15
Pregnancy	1

Adverse event	11
Lost to follow-up	3
Protocol-specified criteria	3
Requirement for alternative therapy	12
Noncompliance	4
Protocol deviation	1

Baseline characteristics

Reporting groups

Reporting group title	Romiplostim

Reporting group description:

Romiplostim was administered to adult participants subcutaneously weekly at doses up to 30 µg/kg based on platelet counts. After Amendment 1 the maximum weekly dose was reduced to 15 µg/kg, and after Amendment 2 the maximum weekly dose was reduced to 10 µg/kg. However, participants enrolled prior to Amendment 2 who were receiving >10 µg/kg were permitted to remain on that higher dose, but could not increase their dose. In addition, if the participant's dose was decreased, it could not be increased to >10 µg/kg.
Romiplostim was administered to pediatric participants subcutaneously weekly at doses up to 10 µg/kg based on platelet counts.

Reporting group values	Romiplostim	Total	
Number of subjects	313	313	
Age categorical Units: Subjects			
Age Continuous Units: Years			
arithmetic mean	51.3		
standard deviation	± 19.7	-	
Gender, Male/Female Units: Participants			
Female	190	190	
Male	123	123	
Race, Customized Units: Subjects			
Black or African American	16	16	
White or Caucasian	259	259	
Hispanic or Latino	25	25	
Asian	9	9	
Japanese	1	1	
American Indian or Alaska Native	1	1	
Native Hawaiian or Other Pacific Islander	1	1	
Other	1	1	

Subject analysis sets

Subject analysis set title	Romiplostim in Adults
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Romiplostim was administered to adult participants subcutaneously weekly at doses up to 30 µg/kg based on platelet counts. After Amendment 1 the maximum weekly dose was reduced to 15 µg/kg, and after Amendment 2 the maximum weekly dose was reduced to 10 µg/kg. However, participants enrolled prior to Amendment 2 who were receiving >10 µg/kg were permitted to remain on that higher dose, but could not increase their dose. In addition, if the participant's dose was decreased, it could not be increased to >10 µg/kg.

Subject analysis set title	Romiplostim in Pediatric Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Romiplostim was administered to pediatric participants subcutaneously weekly at doses up to 10 µg/kg based on platelet counts.

Reporting group values	Romiplostim in Adults	Romiplostim in Pediatric Population	
Number of subjects	292	21	
Age categorical Units: Subjects			
Age Continuous Units: Years			
arithmetic mean	54.2	10.2	
standard deviation	± 16.9	± 5.1	
Gender, Male/Female Units: Participants			
Female	184	6	
Male	108	15	
Race, Customized Units: Subjects			
Black or African American	13	3	
White or Caucasian	246	13	
Hispanic or Latino	21	4	
Asian	9	0	
Japanese	1	0	
American Indian or Alaska Native	1	0	
Native Hawaiian or Other Pacific Islander	1	0	
Other	0	1	

End points

End points reporting groups

Reporting group title	Romiplostim

Reporting group description:

Romiplostim was administered to adult participants subcutaneously weekly at doses up to 30 µg/kg based on platelet counts. After Amendment 1 the maximum weekly dose was reduced to 15 µg/kg, and after Amendment 2 the maximum weekly dose was reduced to 10 µg/kg. However, participants enrolled prior to Amendment 2 who were receiving >10 µg/kg were permitted to remain on that higher dose, but could not increase their dose. In addition, if the participant's dose was decreased, it could not be increased to >10 µg/kg.
Romiplostim was administered to pediatric participants subcutaneously weekly at doses up to 10 µg/kg based on platelet counts.

Subject analysis set title	Romiplostim in Adults
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Romiplostim was administered to adult participants subcutaneously weekly at doses up to 30 µg/kg based on platelet counts. After Amendment 1 the maximum weekly dose was reduced to 15 µg/kg, and after Amendment 2 the maximum weekly dose was reduced to 10 µg/kg. However, participants enrolled prior to Amendment 2 who were receiving >10 µg/kg were permitted to remain on that higher dose, but could not increase their dose. In addition, if the participant's dose was decreased, it could not be increased to >10 µg/kg.

Subject analysis set title	Romiplostim in Pediatric Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Romiplostim was administered to pediatric participants subcutaneously weekly at doses up to 10 µg/kg based on platelet counts.

Primary: Number of Participants with Adverse Events

End point title	Number of Participants with Adverse Events[1]

End point description:

Participants with one or more occurrences of one or more adverse events up to 8 weeks after the end of treatment. Participants with more than one event were only counted once.
This endpoint was analyzed in the Safety Analysis Set, composed of all participants who received at least one dose of romiplostim.

End point type	Primary

End point timeframe:

Duration of treatment plus 8 weeks (up to 285 weeks)

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: The statistical analysis in this open-label extension study was descriptive in nature, no formal hypothesis testing was performed.

End point values	Romiplostim in Adults	Romiplostim in Pediatric Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	291	20		
Units: Participants				
number (not applicable)	284	19		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with a Platelet Response

End point title	Number of Participants with a Platelet Response

End point description:

Platelet response was defined as having a platelet count of ≥ 50 x 10^9/L at any time on study, excluding platelet counts within 8 weeks after receiving any rescue medications.
This endpoint was analyzed in the Efficacy Analysis Set, composed of all enrolled participants who received at least one dose of romiplostim.

End point type	Secondary

End point timeframe:

Duration of treatment (up to 277 weeks)

End point values	Romiplostim in Adults	Romiplostim in Pediatric Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	291	20		
Units: Participants				
number (not applicable)	275	20		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with a Reduction or Discontinuation of Concurrent ITP Therapies

End point title	Number of Participants with a Reduction or Discontinuation of Concurrent ITP Therapies

End point description:

The number of participants with a reduction or discontinuation of concurrent immune (idiopathic) thrombocytopenic purpura (ITP) therapies (corticosteroids, danazol, azathioprine) during the study.
This endpoint was analyzed in the Subset of Efficacy Analysis Set, composed of all enrolled participants who received at least one dose of romiplostim and with baseline concurrent ITP therapy.

End point type	Secondary

End point timeframe:

Duration of treatment (up to 277 weeks)

End point values	Romiplostim in Adults	Romiplostim in Pediatric Population		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	37	2		
Units: Participants				
number (not applicable)	30	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in ITP Patient Assessment Questionnaire

End point title	Change from Baseline in ITP Patient Assessment Questionnaire

End point description:

The ITP Patient Assessment Questionnaire (ITP-PAQ) assesses ITP-specific health-related quality of life (HRQOL). This questionnaire assesses ITP specific health-related quality of life (HRQOL). The questionnaire consists of 44 items and has six domains: These domains assess the impact of ITP on Physical Health, Mental Health, Work, Social Activity, Women's Health and Overall QOL. The impact of ITP on Physical Health consists of four sub-scales, which evaluate ITP related Symptoms, Fatigue, Bother and Activity. The impact of ITP on Mental Health consists of two sub-scales, which evaluate Psychological distress and Fear in a population with ITP. Items are scored from 0-100 with higher scores indicating better HRQOL.
This endpoint was analyzed in the full analysis set with available data.

End point type	Secondary

End point timeframe:

Baseline to Week 48

End point values	Romiplostim in Adults			
Subject group type	Subject analysis set			
Number of subjects analysed	292			
Units: scores on a scale				
arithmetic mean (standard deviation)				
Physical Health Symptoms (N=209)	4.2 (± 13.15)			
Physical Health Fatigue (N=208)	3.99 (± 16)			
Physical Health Bother (N=204)	6.43 (± 17.39)			
Physical Health Activity (N=208)	5.23 (± 21.08)			
Emotional Health Psychological (N=208)	4.01 (± 15.81)			
Emotional Health Fear (N=209)	3.48 (± 12.59)			
Overall Quality of Life (N=210)	8.32 (± 19.65)			
Social Quality of Life (N=209)	3.89 (± 13.41)			
Women's Reproductive Health (N=71)	4.51 (± 16.35)			
Work Quality of Life (N=75)	2.78 (± 14.54)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Short Form 36 (SF-36)

End point title	Change from Baseline in Short Form 36 (SF-36)

End point description:

The SF-36 is a widely used generic health-related quality of life measure. It has 36 questions with 8 domains: Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional and Mental Health. Items are scored from 0 to 100 with higher scores indicating better health status.
This endpoint was analyzed in the full analysis set with available data.

End point type	Secondary

End point timeframe:

Baseline to Week 48

End point values	Romiplostim in Adults			
Subject group type	Subject analysis set			
Number of subjects analysed	292			
Units: scores on a scale				
arithmetic mean (standard deviation)				
Physical Functioning (N=206)	1.38 (± 6.34)			
Role-Physical (N=208)	2.03 (± 8.89)			
Bodily Pain (N=206)	0.94 (± 7.99)			
General Health Perception (N=208)	1.31 (± 7.03)			
Vitality (N=208)	1.68 (± 7.47)			
Social Functioning (N=208)	0.52 (± 8.21)			
Role-Emotional (N=205)	1.75 (± 12.22)			
Mental Health Index (N=208)	0.91 (± 7.45)			
Physical Component Summary (N=200)	1.49 (± 6.51)			
Mental Component Summary (N=200)	1.06 (± 8.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Euroqol-5D (EQ-5D) Index Score

End point title	Change from Baseline in Euroqol-5D (EQ-5D) Index Score

End point description:

The EQ-5D is a patient-completed, multidimensional measure of health related quality of life. The instrument is applicable to a wide range of health conditions and treatments and results in a single index score and a visual analog scale (VAS) score. The EQ-5D descriptive health profile comprises five dimensions of health (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression). Each dimension comprises three levels (no problems, some/moderate problems, extreme problems). A unique EQ-5D health state is defined by combining one level from each of the five dimensions. EQ-5D index values range from -0.59 to 1.00. Higher EQ-5D Index scores represent better health status.
This endpoint was analyzed in the full analysis set with available data.

End point type	Secondary

End point timeframe:

Baseline to Week 48

End point values	Romiplostim in Adults			
Subject group type	Subject analysis set			
Number of subjects analysed	154			
Units: scores on a scale				
arithmetic mean (standard deviation)	0.03 (± 0.16)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Euroqol-5D (EQ-5D) Visual Analogue Scale (VAS)

End point title	Change from Baseline in Euroqol-5D (EQ-5D) Visual Analogue Scale (VAS)

End point description:

The EQ-5D is a patient-completed, multidimensional measure of health related quality of life. The EQ-5D VAS records the respondent's self-rated health status on a vertical graduated (0-100) visual analogue scale. Higher EQ-5D VAS scores represent better health status.
This endpoint was analyzed in the full analysis set with available data.

End point type	Secondary

End point timeframe:

Baseline to Week 48

End point values	Romiplostim in Adults			
Subject group type	Subject analysis set			
Number of subjects analysed	150			
Units: scores on a scale				
arithmetic mean (standard deviation)	6.05 (± 14.85)			

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Assessment

End point title	Patient Global Assessment

End point description:

The Patient Global Assessment is two questions which assess the overall health-related quality of life (HRQOL) and symptoms of the patient. Each item is answered on a 15-point Likert scale ranging from 'A very great deal worse' (1) to 'A very great deal better' (15). A higher score indicates that quality of life or symptoms have improved.
This endpoint was analyzed in the full analysis set with available data.

End point type	Secondary

End point timeframe:

Week 1 and Week 48

End point values	Romiplostim in Adults			
Subject group type	Subject analysis set			
Number of subjects analysed	292			
Units: scores on a scale				
arithmetic mean (standard deviation)				
Week 1 (N=271) Week 48 (N=216)	7.61 (± 2.02) 8.18 (± 1.78)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For adult participants the average duration was 110 weeks; for pediatric participants the average duration is 82 weeks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Romiplostim in Pediatric Population

Reporting group description:

Romiplostim administered to pediatric participants subcutaneously weekly at doses up to 10 µg/kg based on platelet counts.

Reporting group title	Romiplostim in Adults

Reporting group description:

Romiplostim administered to adult participants subcutaneously weekly at doses up to 30 µg/kg based on platelet counts. After Amendment 1 the maximum weekly dose was reduced to 15 µg/kg, and after Amendment 2 the maximum weekly dose was reduced to 10 µg/kg. However, participants enrolled prior to Amendment 2 who were receiving >10 µg/kg were permitted to remain on that higher dose, but could not increase their dose. In addition, if the participant's dose was decreased, it could not be increased to >10 µg/kg.

Serious adverse events	Romiplostim in Pediatric Population	Romiplostim in Adults	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 20 (10.00%)	117 / 291 (40.21%)	
number of deaths (all causes)	0	16	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic lymphocytic leukaemia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colon cancer recurrent			

subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic neoplasm malignant			
subjects affected / exposed	0 / 20 (0.00%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lung neoplasm malignant			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Lymphoma			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metastases to central nervous system			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple myeloma			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelofibrosis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasm of orbit			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal cell carcinoma			

subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transitional cell carcinoma			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Deep vein thrombosis			
subjects affected / exposed	0 / 20 (0.00%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral arterial stenosis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Phlebitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subgaleal haematoma			

subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombosis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Cholecystectomy			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Elective surgery			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Knee arthroplasty			
subjects affected / exposed	0 / 20 (0.00%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Plastic surgery			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin cosmetic procedure			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stent placement			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			

Abortion spontaneous			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Adverse drug reaction			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthenia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chest pain			
subjects affected / exposed	0 / 20 (0.00%)	3 / 291 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Fatigue			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised oedema			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hernia obstructive			
subjects affected / exposed	0 / 20 (0.00%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperpyrexia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mechanical complication of implant			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	0 / 20 (0.00%)	4 / 291 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metrorrhagia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Ovarian cyst			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vaginal haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Acute pulmonary oedema			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Asthma			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cough			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	0 / 20 (0.00%)	4 / 291 (1.37%)	
occurrences causally related to treatment / all	0 / 0	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	1 / 20 (5.00%)	3 / 291 (1.03%)	
occurrences causally related to treatment / all	0 / 1	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Pleuritic pain			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory arrest			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 20 (0.00%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Agitation			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anxiety			
subjects affected / exposed	0 / 20 (0.00%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Confusional state			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mental status changes			

subjects affected / exposed	0 / 20 (0.00%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Suicidal ideation			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Megakaryocytes increased			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count decreased			
subjects affected / exposed	0 / 20 (0.00%)	3 / 291 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Platelet count increased			
subjects affected / exposed	0 / 20 (0.00%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Arteriovenous fistula site complication			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fractured sacrum			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Head injury			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 20 (0.00%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Humerus fracture			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incisional hernia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Medical device complication			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meniscus lesion			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper limb fracture			

subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Congenital, familial and genetic disorders			
Atrial septal defect			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 20 (0.00%)	3 / 291 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Angina unstable			
subjects affected / exposed	0 / 20 (0.00%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	1 / 1	
Atrial fibrillation			
subjects affected / exposed	0 / 20 (0.00%)	3 / 291 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Cardiac failure			
subjects affected / exposed	0 / 20 (0.00%)	4 / 291 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cardiac failure congestive			
subjects affected / exposed	0 / 20 (0.00%)	5 / 291 (1.72%)	
occurrences causally related to treatment / all	0 / 0	1 / 13	
deaths causally related to treatment / all	0 / 0	0 / 2	
Cardiac tamponade			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Coronary artery disease			
subjects affected / exposed	0 / 20 (0.00%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	0 / 20 (0.00%)	5 / 291 (1.72%)	
occurrences causally related to treatment / all	0 / 0	2 / 5	
deaths causally related to treatment / all	0 / 0	1 / 3	
Pericardial haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Trifascicular block			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	0 / 20 (0.00%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Complex regional pain syndrome			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Convulsion			

subjects affected / exposed	0 / 20 (0.00%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intracranial aneurysm			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Loss of consciousness			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Migraine			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multiple sclerosis relapse			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Presyncope			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	0 / 20 (0.00%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			

subjects affected / exposed	0 / 20 (0.00%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transverse sinus thrombosis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 20 (0.00%)	3 / 291 (1.03%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bicytopenia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow disorder			
subjects affected / exposed	0 / 20 (0.00%)	4 / 291 (1.37%)	
occurrences causally related to treatment / all	0 / 0	4 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone marrow reticulin fibrosis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Evans syndrome			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic anaemia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Idiopathic thrombocytopenic purpura			

subjects affected / exposed	1 / 20 (5.00%)	7 / 291 (2.41%)	
occurrences causally related to treatment / all	0 / 1	2 / 16	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	0 / 20 (0.00%)	23 / 291 (7.90%)	
occurrences causally related to treatment / all	0 / 0	5 / 31	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	0 / 20 (0.00%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vestibular disorder			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Blindness			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Conjunctival haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Papilloedema			

subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain			
subjects affected / exposed	0 / 20 (0.00%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain lower			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Anal fistula			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ascites			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis			
subjects affected / exposed	0 / 20 (0.00%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Colitis ischaemic			

subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Femoral hernia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	4 / 291 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingival bleeding			
subjects affected / exposed	0 / 20 (0.00%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Irritable bowel syndrome			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth cyst			

subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth ulceration			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nausea			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Periodontitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Small intestinal obstruction			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth impacted			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth loss			

subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Biliary colic			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis			
subjects affected / exposed	0 / 20 (0.00%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholecystitis acute			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 20 (0.00%)	3 / 291 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic failure			
subjects affected / exposed	0 / 20 (0.00%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic steatosis			

subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Portal vein thrombosis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Blister			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ecchymosis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Petechiae			
subjects affected / exposed	0 / 20 (0.00%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psoriasis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Purpura			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rash			

subjects affected / exposed	0 / 20 (0.00%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Systemic lupus erythematosus rash			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urticaria			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	0 / 20 (0.00%)	3 / 291 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 1	
Renal failure acute			
subjects affected / exposed	0 / 20 (0.00%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal failure chronic			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary bladder polyp			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary retention			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			

Arthritis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Intervertebral disc protrusion			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	0 / 20 (0.00%)	3 / 291 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain in extremity			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rhabdomyolysis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Appendicitis			
subjects affected / exposed	0 / 20 (0.00%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bacteraemia			

subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	0 / 20 (0.00%)	3 / 291 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Candidiasis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter bacteraemia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Catheter related infection			
subjects affected / exposed	0 / 20 (0.00%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	0 / 20 (0.00%)	3 / 291 (1.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device related infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epiglottitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Influenza			
subjects affected / exposed	1 / 20 (5.00%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Klebsiella sepsis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Localised infection			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Meningitis listeria			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Nasopharyngitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Parotitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pharyngitis streptococcal			

subjects affected / exposed	1 / 20 (5.00%)	0 / 291 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumococcal sepsis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pneumonia			
subjects affected / exposed	0 / 20 (0.00%)	8 / 291 (2.75%)	
occurrences causally related to treatment / all	0 / 0	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia streptococcal			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Post procedural cellulitis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Progressive multifocal leukoencephalopathy			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Sepsis			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombophlebitis septic			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tooth abscess			

subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	0 / 20 (0.00%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dehydration			
subjects affected / exposed	0 / 20 (0.00%)	4 / 291 (1.37%)	
occurrences causally related to treatment / all	0 / 0	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyperkalaemia			
subjects affected / exposed	0 / 20 (0.00%)	2 / 291 (0.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypokalaemia			
subjects affected / exposed	0 / 20 (0.00%)	1 / 291 (0.34%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Romiplostim in Pediatric Population	Romiplostim in Adults	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	19 / 20 (95.00%)	272 / 291 (93.47%)	
Vascular disorders			
Flushing			
subjects affected / exposed	1 / 20 (5.00%)	2 / 291 (0.69%)	
occurrences (all)	1	2	

Haematoma			
subjects affected / exposed	1 / 20 (5.00%)	37 / 291 (12.71%)	
occurrences (all)	1	95	
Haemorrhage			
subjects affected / exposed	1 / 20 (5.00%)	10 / 291 (3.44%)	
occurrences (all)	1	10	
Hypertension			
subjects affected / exposed	0 / 20 (0.00%)	17 / 291 (5.84%)	
occurrences (all)	0	19	
Surgical and medical procedures			
Ear tube insertion			
subjects affected / exposed	1 / 20 (5.00%)	0 / 291 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 20 (0.00%)	22 / 291 (7.56%)	
occurrences (all)	0	31	
Chest pain			
subjects affected / exposed	1 / 20 (5.00%)	16 / 291 (5.50%)	
occurrences (all)	2	20	
Chills			
subjects affected / exposed	2 / 20 (10.00%)	12 / 291 (4.12%)	
occurrences (all)	2	18	
Fatigue			
subjects affected / exposed	7 / 20 (35.00%)	93 / 291 (31.96%)	
occurrences (all)	8	247	
Influenza like illness			
subjects affected / exposed	1 / 20 (5.00%)	9 / 291 (3.09%)	
occurrences (all)	1	9	
Injection site haematoma			
subjects affected / exposed	0 / 20 (0.00%)	15 / 291 (5.15%)	
occurrences (all)	0	29	
Injection site haemorrhage			
subjects affected / exposed	1 / 20 (5.00%)	1 / 291 (0.34%)	
occurrences (all)	1	1	
Injection site pain			

subjects affected / exposed	1 / 20 (5.00%)	12 / 291 (4.12%)	
occurrences (all)	1	17	
Local swelling			
subjects affected / exposed	1 / 20 (5.00%)	1 / 291 (0.34%)	
occurrences (all)	1	1	
Oedema peripheral			
subjects affected / exposed	0 / 20 (0.00%)	41 / 291 (14.09%)	
occurrences (all)	0	83	
Pain			
subjects affected / exposed	4 / 20 (20.00%)	32 / 291 (11.00%)	
occurrences (all)	4	51	
Pyrexia			
subjects affected / exposed	9 / 20 (45.00%)	36 / 291 (12.37%)	
occurrences (all)	13	54	
Swelling			
subjects affected / exposed	1 / 20 (5.00%)	0 / 291 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 20 (5.00%)	12 / 291 (4.12%)	
occurrences (all)	1	12	
Latex allergy			
subjects affected / exposed	1 / 20 (5.00%)	0 / 291 (0.00%)	
occurrences (all)	1	0	
Seasonal allergy			
subjects affected / exposed	1 / 20 (5.00%)	16 / 291 (5.50%)	
occurrences (all)	1	33	
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	1 / 20 (5.00%)	14 / 291 (4.81%)	
occurrences (all)	1	18	
Vaginal haemorrhage			
subjects affected / exposed	1 / 20 (5.00%)	13 / 291 (4.47%)	
occurrences (all)	2	19	
Respiratory, thoracic and mediastinal disorders			

Asthma			
subjects affected / exposed	1 / 20 (5.00%)	7 / 291 (2.41%)	
occurrences (all)	3	13	
Cough			
subjects affected / exposed	9 / 20 (45.00%)	70 / 291 (24.05%)	
occurrences (all)	20	130	
Dyspnoea			
subjects affected / exposed	2 / 20 (10.00%)	22 / 291 (7.56%)	
occurrences (all)	2	36	
Epistaxis			
subjects affected / exposed	5 / 20 (25.00%)	73 / 291 (25.09%)	
occurrences (all)	6	228	
Nasal congestion			
subjects affected / exposed	6 / 20 (30.00%)	30 / 291 (10.31%)	
occurrences (all)	9	60	
Nasal turbinate abnormality			
subjects affected / exposed	1 / 20 (5.00%)	0 / 291 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal blistering			
subjects affected / exposed	0 / 20 (0.00%)	20 / 291 (6.87%)	
occurrences (all)	0	74	
Oropharyngeal pain			
subjects affected / exposed	6 / 20 (30.00%)	50 / 291 (17.18%)	
occurrences (all)	8	81	
Pharyngeal erythema			
subjects affected / exposed	1 / 20 (5.00%)	0 / 291 (0.00%)	
occurrences (all)	1	0	
Productive cough			
subjects affected / exposed	1 / 20 (5.00%)	5 / 291 (1.72%)	
occurrences (all)	1	5	
Respiratory tract congestion			
subjects affected / exposed	1 / 20 (5.00%)	9 / 291 (3.09%)	
occurrences (all)	1	22	
Rhinorrhoea			
subjects affected / exposed	5 / 20 (25.00%)	26 / 291 (8.93%)	
occurrences (all)	7	71	

Wheezing			
subjects affected / exposed	1 / 20 (5.00%)	5 / 291 (1.72%)	
occurrences (all)	1	5	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 20 (0.00%)	21 / 291 (7.22%)	
occurrences (all)	0	23	
Depressed mood			
subjects affected / exposed	1 / 20 (5.00%)	0 / 291 (0.00%)	
occurrences (all)	1	0	
Depression			
subjects affected / exposed	0 / 20 (0.00%)	19 / 291 (6.53%)	
occurrences (all)	0	25	
Emotional disorder			
subjects affected / exposed	1 / 20 (5.00%)	0 / 291 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	0 / 20 (0.00%)	41 / 291 (14.09%)	
occurrences (all)	0	51	
Investigations			
Breath sounds abnormal			
subjects affected / exposed	1 / 20 (5.00%)	1 / 291 (0.34%)	
occurrences (all)	1	1	
Streptococcal identification test positive			
subjects affected / exposed	1 / 20 (5.00%)	0 / 291 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	2 / 20 (10.00%)	3 / 291 (1.03%)	
occurrences (all)	2	3	
Arthropod bite			
subjects affected / exposed	2 / 20 (10.00%)	6 / 291 (2.06%)	
occurrences (all)	3	6	
Contusion			
subjects affected / exposed	8 / 20 (40.00%)	88 / 291 (30.24%)	
occurrences (all)	18	336	

Excoriation			
subjects affected / exposed	3 / 20 (15.00%)	10 / 291 (3.44%)	
occurrences (all)	4	12	
Eye injury			
subjects affected / exposed	1 / 20 (5.00%)	7 / 291 (2.41%)	
occurrences (all)	1	7	
Fall			
subjects affected / exposed	0 / 20 (0.00%)	19 / 291 (6.53%)	
occurrences (all)	0	28	
Joint sprain			
subjects affected / exposed	2 / 20 (10.00%)	11 / 291 (3.78%)	
occurrences (all)	2	12	
Laceration			
subjects affected / exposed	1 / 20 (5.00%)	1 / 291 (0.34%)	
occurrences (all)	1	1	
Limb injury			
subjects affected / exposed	1 / 20 (5.00%)	4 / 291 (1.37%)	
occurrences (all)	1	5	
Muscle strain			
subjects affected / exposed	1 / 20 (5.00%)	4 / 291 (1.37%)	
occurrences (all)	1	4	
Nerve injury			
subjects affected / exposed	1 / 20 (5.00%)	0 / 291 (0.00%)	
occurrences (all)	1	0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 20 (5.00%)	3 / 291 (1.03%)	
occurrences (all)	1	3	
Procedural pain			
subjects affected / exposed	2 / 20 (10.00%)	17 / 291 (5.84%)	
occurrences (all)	2	18	
Scratch			
subjects affected / exposed	1 / 20 (5.00%)	4 / 291 (1.37%)	
occurrences (all)	3	4	
Skin laceration			
subjects affected / exposed	0 / 20 (0.00%)	18 / 291 (6.19%)	
occurrences (all)	0	19	

Traumatic haemorrhage			
subjects affected / exposed	1 / 20 (5.00%)	0 / 291 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Cerebral haematoma			
subjects affected / exposed	1 / 20 (5.00%)	0 / 291 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	2 / 20 (10.00%)	51 / 291 (17.53%)	
occurrences (all)	3	78	
Headache			
subjects affected / exposed	9 / 20 (45.00%)	109 / 291 (37.46%)	
occurrences (all)	17	411	
Hypoaesthesia			
subjects affected / exposed	1 / 20 (5.00%)	12 / 291 (4.12%)	
occurrences (all)	1	15	
Migraine			
subjects affected / exposed	1 / 20 (5.00%)	15 / 291 (5.15%)	
occurrences (all)	1	21	
Paraesthesia			
subjects affected / exposed	0 / 20 (0.00%)	28 / 291 (9.62%)	
occurrences (all)	0	35	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 20 (5.00%)	17 / 291 (5.84%)	
occurrences (all)	1	20	
Anaemia megaloblastic			
subjects affected / exposed	1 / 20 (5.00%)	0 / 291 (0.00%)	
occurrences (all)	1	0	
Idiopathic thrombocytopenic purpura			
subjects affected / exposed	2 / 20 (10.00%)	29 / 291 (9.97%)	
occurrences (all)	2	51	
Lymphadenopathy			
subjects affected / exposed	1 / 20 (5.00%)	4 / 291 (1.37%)	
occurrences (all)	1	4	
Ear and labyrinth disorders			

Ear pain			
subjects affected / exposed	1 / 20 (5.00%)	13 / 291 (4.47%)	
occurrences (all)	1	16	
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	1 / 20 (5.00%)	7 / 291 (2.41%)	
occurrences (all)	1	8	
Conjunctival oedema			
subjects affected / exposed	1 / 20 (5.00%)	0 / 291 (0.00%)	
occurrences (all)	1	0	
Lacrimation increased			
subjects affected / exposed	1 / 20 (5.00%)	2 / 291 (0.69%)	
occurrences (all)	1	3	
Photophobia			
subjects affected / exposed	1 / 20 (5.00%)	0 / 291 (0.00%)	
occurrences (all)	1	0	
Scleral haemorrhage			
subjects affected / exposed	1 / 20 (5.00%)	0 / 291 (0.00%)	
occurrences (all)	1	0	
Vision blurred			
subjects affected / exposed	1 / 20 (5.00%)	8 / 291 (2.75%)	
occurrences (all)	1	10	
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 20 (5.00%)	17 / 291 (5.84%)	
occurrences (all)	2	18	
Abdominal pain			
subjects affected / exposed	3 / 20 (15.00%)	33 / 291 (11.34%)	
occurrences (all)	3	53	
Abdominal pain upper			
subjects affected / exposed	4 / 20 (20.00%)	21 / 291 (7.22%)	
occurrences (all)	18	26	
Chapped lips			
subjects affected / exposed	1 / 20 (5.00%)	1 / 291 (0.34%)	
occurrences (all)	1	1	
Constipation			

subjects affected / exposed	1 / 20 (5.00%)	26 / 291 (8.93%)	
occurrences (all)	2	30	
Diarrhoea			
subjects affected / exposed	2 / 20 (10.00%)	72 / 291 (24.74%)	
occurrences (all)	2	129	
Dyspepsia			
subjects affected / exposed	0 / 20 (0.00%)	19 / 291 (6.53%)	
occurrences (all)	0	21	
Gastric disorder			
subjects affected / exposed	1 / 20 (5.00%)	0 / 291 (0.00%)	
occurrences (all)	1	0	
Gingival bleeding			
subjects affected / exposed	5 / 20 (25.00%)	43 / 291 (14.78%)	
occurrences (all)	7	74	
Haematemesis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 291 (0.00%)	
occurrences (all)	2	0	
Lip dry			
subjects affected / exposed	1 / 20 (5.00%)	0 / 291 (0.00%)	
occurrences (all)	1	0	
Lip haemorrhage			
subjects affected / exposed	1 / 20 (5.00%)	3 / 291 (1.03%)	
occurrences (all)	1	3	
Mouth haemorrhage			
subjects affected / exposed	4 / 20 (20.00%)	21 / 291 (7.22%)	
occurrences (all)	4	36	
Mouth ulceration			
subjects affected / exposed	2 / 20 (10.00%)	4 / 291 (1.37%)	
occurrences (all)	2	4	
Nausea			
subjects affected / exposed	4 / 20 (20.00%)	69 / 291 (23.71%)	
occurrences (all)	4	113	
Stomatitis			
subjects affected / exposed	1 / 20 (5.00%)	9 / 291 (3.09%)	
occurrences (all)	1	26	
Tongue haematoma			

subjects affected / exposed	1 / 20 (5.00%)	0 / 291 (0.00%)	
occurrences (all)	1	0	
Tooth socket haemorrhage			
subjects affected / exposed	1 / 20 (5.00%)	2 / 291 (0.69%)	
occurrences (all)	1	2	
Toothache			
subjects affected / exposed	1 / 20 (5.00%)	17 / 291 (5.84%)	
occurrences (all)	1	27	
Vomiting			
subjects affected / exposed	7 / 20 (35.00%)	46 / 291 (15.81%)	
occurrences (all)	14	64	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 20 (5.00%)	6 / 291 (2.06%)	
occurrences (all)	1	8	
Blood blister			
subjects affected / exposed	0 / 20 (0.00%)	19 / 291 (6.53%)	
occurrences (all)	0	40	
Dermatitis			
subjects affected / exposed	1 / 20 (5.00%)	7 / 291 (2.41%)	
occurrences (all)	1	8	
Ecchymosis			
subjects affected / exposed	1 / 20 (5.00%)	25 / 291 (8.59%)	
occurrences (all)	1	35	
Erythema			
subjects affected / exposed	1 / 20 (5.00%)	12 / 291 (4.12%)	
occurrences (all)	1	14	
Petechiae			
subjects affected / exposed	9 / 20 (45.00%)	53 / 291 (18.21%)	
occurrences (all)	18	99	
Pigmentation disorder			
subjects affected / exposed	1 / 20 (5.00%)	0 / 291 (0.00%)	
occurrences (all)	1	0	
Pruritus			
subjects affected / exposed	0 / 20 (0.00%)	23 / 291 (7.90%)	
occurrences (all)	0	45	

Rash			
subjects affected / exposed	5 / 20 (25.00%)	44 / 291 (15.12%)	
occurrences (all)	7	62	
Rash generalised			
subjects affected / exposed	1 / 20 (5.00%)	1 / 291 (0.34%)	
occurrences (all)	1	1	
Scab			
subjects affected / exposed	2 / 20 (10.00%)	0 / 291 (0.00%)	
occurrences (all)	2	0	
Skin discolouration			
subjects affected / exposed	1 / 20 (5.00%)	4 / 291 (1.37%)	
occurrences (all)	1	4	
Skin lesion			
subjects affected / exposed	1 / 20 (5.00%)	18 / 291 (6.19%)	
occurrences (all)	1	24	
Swelling face			
subjects affected / exposed	1 / 20 (5.00%)	6 / 291 (2.06%)	
occurrences (all)	1	6	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 20 (0.00%)	15 / 291 (5.15%)	
occurrences (all)	0	16	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 20 (25.00%)	69 / 291 (23.71%)	
occurrences (all)	6	156	
Back pain			
subjects affected / exposed	1 / 20 (5.00%)	54 / 291 (18.56%)	
occurrences (all)	2	78	
Groin pain			
subjects affected / exposed	1 / 20 (5.00%)	1 / 291 (0.34%)	
occurrences (all)	1	1	
Joint swelling			
subjects affected / exposed	0 / 20 (0.00%)	16 / 291 (5.50%)	
occurrences (all)	0	18	
Muscle spasms			

subjects affected / exposed	1 / 20 (5.00%)	28 / 291 (9.62%)	
occurrences (all)	1	62	
Musculoskeletal pain			
subjects affected / exposed	1 / 20 (5.00%)	29 / 291 (9.97%)	
occurrences (all)	1	44	
Myalgia			
subjects affected / exposed	3 / 20 (15.00%)	35 / 291 (12.03%)	
occurrences (all)	3	48	
Neck pain			
subjects affected / exposed	1 / 20 (5.00%)	7 / 291 (2.41%)	
occurrences (all)	1	11	
Nodule on extremity			
subjects affected / exposed	1 / 20 (5.00%)	1 / 291 (0.34%)	
occurrences (all)	1	1	
Pain in extremity			
subjects affected / exposed	2 / 20 (10.00%)	55 / 291 (18.90%)	
occurrences (all)	6	97	
Infections and infestations			
Anogenital warts			
subjects affected / exposed	1 / 20 (5.00%)	0 / 291 (0.00%)	
occurrences (all)	1	0	
Bronchiolitis			
subjects affected / exposed	1 / 20 (5.00%)	0 / 291 (0.00%)	
occurrences (all)	1	0	
Bronchitis			
subjects affected / exposed	1 / 20 (5.00%)	22 / 291 (7.56%)	
occurrences (all)	1	37	
Conjunctivitis infective			
subjects affected / exposed	1 / 20 (5.00%)	0 / 291 (0.00%)	
occurrences (all)	1	0	
Ear infection			
subjects affected / exposed	2 / 20 (10.00%)	11 / 291 (3.78%)	
occurrences (all)	2	18	
Gastroenteritis			
subjects affected / exposed	2 / 20 (10.00%)	13 / 291 (4.47%)	
occurrences (all)	2	16	

Gastroenteritis viral			
subjects affected / exposed	1 / 20 (5.00%)	5 / 291 (1.72%)	
occurrences (all)	1	5	
Hepatitis B			
subjects affected / exposed	1 / 20 (5.00%)	0 / 291 (0.00%)	
occurrences (all)	1	0	
Influenza			
subjects affected / exposed	0 / 20 (0.00%)	23 / 291 (7.90%)	
occurrences (all)	0	32	
Nasopharyngitis			
subjects affected / exposed	5 / 20 (25.00%)	100 / 291 (34.36%)	
occurrences (all)	7	185	
Oral herpes			
subjects affected / exposed	1 / 20 (5.00%)	6 / 291 (2.06%)	
occurrences (all)	2	12	
Pharyngitis			
subjects affected / exposed	1 / 20 (5.00%)	14 / 291 (4.81%)	
occurrences (all)	1	17	
Pharyngitis streptococcal			
subjects affected / exposed	1 / 20 (5.00%)	1 / 291 (0.34%)	
occurrences (all)	1	1	
Pneumonia			
subjects affected / exposed	1 / 20 (5.00%)	6 / 291 (2.06%)	
occurrences (all)	1	9	
Rash pustular			
subjects affected / exposed	1 / 20 (5.00%)	1 / 291 (0.34%)	
occurrences (all)	1	1	
Sinusitis			
subjects affected / exposed	1 / 20 (5.00%)	38 / 291 (13.06%)	
occurrences (all)	1	63	
Streptococcal infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 291 (0.00%)	
occurrences (all)	1	0	
Subcutaneous abscess			
subjects affected / exposed	1 / 20 (5.00%)	0 / 291 (0.00%)	
occurrences (all)	1	0	

Tinea infection			
subjects affected / exposed	1 / 20 (5.00%)	0 / 291 (0.00%)	
occurrences (all)	1	0	
Tooth infection			
subjects affected / exposed	1 / 20 (5.00%)	8 / 291 (2.75%)	
occurrences (all)	1	10	
Upper respiratory tract infection			
subjects affected / exposed	10 / 20 (50.00%)	76 / 291 (26.12%)	
occurrences (all)	16	136	
Urinary tract infection			
subjects affected / exposed	0 / 20 (0.00%)	36 / 291 (12.37%)	
occurrences (all)	0	53	
Varicella			
subjects affected / exposed	1 / 20 (5.00%)	1 / 291 (0.34%)	
occurrences (all)	1	1	
Viral infection			
subjects affected / exposed	2 / 20 (10.00%)	5 / 291 (1.72%)	
occurrences (all)	3	7	
Viral upper respiratory tract infection			
subjects affected / exposed	3 / 20 (15.00%)	7 / 291 (2.41%)	
occurrences (all)	4	7	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 20 (5.00%)	14 / 291 (4.81%)	
occurrences (all)	1	14	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 February 2005	The major changes were: • Self-injection of romiplostim was allowed for subjects on a stable dose of romiplostim. • Dose adjustment and concomitant medications rules were adjusted to allow a scenario more representative of real-life practice, and to give the investigator more flexibility in treating subjects. • Maximum permitted dose of romiplostim was reduced from 30 µg/kg to 15 µg/kg. • Subjects were asked to consent to an optional bone marrow aspirate and biopsy at study entry to assess changes in the bone marrow before continuing romiplostim treatment.
23 May 2006	The major changes were: • The drawing and analyzing of additional blood samples for antibody analysis at the request of the investigator or Amgen was allowed. • It was clarified that self-injecting subjects were not required to have weekly platelet counts; subjects who were self-injecting were to have platelet counts assessed every 4 weeks. • Rather than stating specific previous romiplostim ITP studies from which subjects could subsequently enroll into the present study, it was stated that subjects who completed any romiplostim ITP study could enroll into this study; this change allowed subjects in Study 20040209 (Individual Patient Protocol) to transfer into this study. • Maximum permitted dose of romiplostim was reduced from 15 µg/kg to 10 µg/kg. Accumulating data from Study 20020213 indicated that most subjects responded at doses < 10 µg/kg and that subjects not responding at a dose of ≥ 10 µg/kg did not derive additional benefit with a higher dose. • It was specified that for assessment of anti-romiplostim antibody status at screening, a subject's blood sample from his/her previous study's EOS visit could be used regardless of the duration since the sample was taken, and that the result of the antibody test was not required prior to enrollment in Study 20030213. • Subjects whose platelet counts remained ≤ 20 x 109/L after receiving romiplostim at ≥ 10 µg/kg for 4 consecutive weeks had to be discontinued from the study. • The signing of informed consent for a subject by a legally acceptable representative was no longer allowed because Amgen's current policy stated that only the subject could sign informed consent in studies with PRO end points. • The Risks & Discomforts section of the Informed Consent Template was revised.
18 October 2007	The major changes were: • Updated the protocol to allow for the transfer of pediatric subjects from protocol 20050195 to protocol 20030213, including instructions on dosing of romiplostim in pediatric subjects and dilution of romiplostim. Additional background information on ITP in pediatric patients was also included. • Updated the Dose Adjustment Rules to accurately reflect the current dosing of romiplostim in ITP subjects. • Removed the requirements for subjects to wait until platelet counts had fallen to < 50 x 109/L and to wash out of certain ITP treatments prior to study enrollment. This allowed subjects to enroll into protocol 20030213 immediately after completing their previous romiplostim ITP study. • Clarified and updated the timing of protocol-required procedures and assessments. • Updated the Statistical section of the protocol, including the subset analyses to be completed, the analysis for platelet response, and the analysis in the PRO end points.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported