Clinical trial results:
A Randomized, Double Blind, Placebo Controlled Study Evaluating the Efficacy and Safety of Romiplostim Treatment of Thrombocytopenia in Subjects with Low or Intermediate-1 Risk Myelodysplastic Syndrome (MDS)

Summary

EudraCT number	2007-007258-75
Trial protocol	ES SK NL CZ IE AT DE HU BE GB DK SE FR IT PL
Global end of trial date	10 December 2015

Results information

Result version number	v1 (current)
This version publication date	15 December 2016
First version publication date	15 December 2016

Trial information

Trial identification

Sponsor protocol code	20060198

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00614523
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)	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	10 December 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	10 December 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of romiplostim for the treatment of thrombocytopenia in subjects with international prognostic scoring system (IPSS) low or intermediate-1 (INT-1) risk MDS as measured by the number of clinically significant bleeding events (CSBEs).

Protection of trial subjects:

This study was conducted in accordance with International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.
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	21 July 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy
Long term follow-up duration	60 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 9
Country: Number of subjects enrolled	United States: 23
Country: Number of subjects enrolled	Australia: 13
Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Belgium: 17
Country: Number of subjects enrolled	Czech Republic: 23
Country: Number of subjects enrolled	France: 23
Country: Number of subjects enrolled	Germany: 35
Country: Number of subjects enrolled	Hungary: 8
Country: Number of subjects enrolled	Ireland: 3
Country: Number of subjects enrolled	Italy: 24
Country: Number of subjects enrolled	Netherlands: 5
Country: Number of subjects enrolled	Poland: 11
Country: Number of subjects enrolled	Russian Federation: 13

Country: Number of subjects enrolled	Slovakia: 4
Country: Number of subjects enrolled	Spain: 18
Country: Number of subjects enrolled	Switzerland: 6
Country: Number of subjects enrolled	United Kingdom: 12
Worldwide total number of subjects	250
EEA total number of subjects	186

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)	80
From 65 to 84 years	163
85 years and over	7

Subject disposition

Recruitment

Recruitment details:

First Subject Enrolled: 21 July 2008, Last Subject Enrolled: 16 December 2010.

Pre-assignment

Screening details:

The study enrolled subjects with thrombocytopenia with IPSS low or INT-1 risk MDS. Participants were randomized in a 2:1 ratio to receive romiplostim 750 µg or placebo. Randomization was stratified by baseline platelet count (≥ 20 x 10^9/L or < 20 x 10^9/L) and by baseline IPSS rating (low or INT-1).

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Weekly subcutaneous dosing with blinded matching placebo dose level for 26 weeks during the Test Treatment Period and for 24 weeks during the Extended Treatment Period, separated by a 4-week interim washout period.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered by subcutaneous injection weekly

Arm title	Romiplostim

Arm description:

Weekly subcutaneous dosing based on platelet count for 26 weeks during the Test Treatment Period and for 24 weeks during the Extended Treatment Period, separated by a 4-week interim washout period. Starting dose was 750 µg, up to a maximum dose of 1000 µg, or reduced to a minimum of 250 µg.

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 weekly

Number of subjects in period 1	Placebo	Romiplostim
Started	83	167
Completed	20	36
Not completed	63	131
Consent withdrawn by subject	12	22
Disease progression	-	8
Administrative decision	23	46
Adverse event, non-fatal	4	20
Other	6	11
Death	5	8
Protocol deviation	3	2
Ineligibility determined	1	2
Lost to follow-up	-	1
Requirement for alternative therapy	9	11

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Weekly subcutaneous dosing with blinded matching placebo dose level for 26 weeks during the Test Treatment Period and for 24 weeks during the Extended Treatment Period, separated by a 4-week interim washout period.	
Reporting group title	Romiplostim
Reporting group description:	
Weekly subcutaneous dosing based on platelet count for 26 weeks during the Test Treatment Period and for 24 weeks during the Extended Treatment Period, separated by a 4-week interim washout period. Starting dose was 750 µg, up to a maximum dose of 1000 µg, or reduced to a minimum of 250 µg.	

Reporting group values	Placebo	Romiplostim	Total
Number of subjects	83	167	250
Age Categorical Units: Subjects			
< 65 years	28	52	80
≥ 65 years	55	115	170
Age Continuous Units: years			
arithmetic mean	67	68.4	
standard deviation	± 11.5	± 12	-
Gender Categorical Units: Subjects			
Female	30	72	102
Male	53	95	148
Race Units: Subjects			
White or Caucasian	79	156	235
Black or African American	0	1	1
Hispanic or Latino	1	4	5
Asian	1	1	2
Other	2	5	7
Myelodysplastic Syndromes WHO Classification			
RA: Refractory Anemia RAEB-1: Refractory Anemia with Excess Blasts-1 RAEB-2: Refractory Anemia with Excess Blasts-2 RARS: Refractory Anemia with Ringed Sideroblasts RCMD: Refractory cytopenia with multilineage dysplasia RCMD-RS: Refractory cytopenia with multilineage dysplasia and ringed sideroblasts MDS-U: Myelodysplastic syndrome – unclassified MDS associated with isolated del(5q).			
Units: Subjects			
RA	5	6	11
RARS	0	2	2
RAEB-1	9	24	33
RAEB-2	0	1	1
RCMD	55	114	169
RCMD-RS	2	4	6
MDS-U	12	16	28
MDS associated with isolated del 5Q	0	0	0
Prior MDS Therapy			

Units: Subjects			
No	70	133	203
Yes	13	34	47
International Prognostic Scoring System (IPSS) Total Score			
The MDS IPSS assesses the severity of MDS based on 3 prognostic factors each assigned a score: the proportion of bone marrow blasts, chromosome changes in the marrow cells (karyotype) and the presence of one or more low blood cell counts (cytopenias). The IPSS score is the sum of the bone marrow blast + karyotype + cytopenia score and ranges from 0 (low risk) to 3.5 (high risk). Prognosis is categorized as Low risk (score = 0), Intermediate-1 (score 0.5 to 1.0), Intermediate-2 (score 1.5 to 2.0) or High risk (score ≥ 2.5).			
Units: Subjects			
0 (Low risk)	23	40	63
0.5 (Intermediate-1 risk)	38	86	124
1 (Intermediate-1 risk)	20	34	54
1.5 (Intermediate-2 risk)	0	1	1
Missing	2	6	8
Baseline Platelet Counts			
Units: 10^9/L			
arithmetic mean	21.5	22.3	
standard deviation	± 13	± 11.5	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Weekly subcutaneous dosing with blinded matching placebo dose level for 26 weeks during the Test Treatment Period and for 24 weeks during the Extended Treatment Period, separated by a 4-week interim washout period.	
Reporting group title	Romiplostim
Reporting group description:	
Weekly subcutaneous dosing based on platelet count for 26 weeks during the Test Treatment Period and for 24 weeks during the Extended Treatment Period, separated by a 4-week interim washout period. Starting dose was 750 µg, up to a maximum dose of 1000 µg, or reduced to a minimum of 250 µg.	

Primary: Number of Clinically Significant Bleeding Events

End point title	Number of Clinically Significant Bleeding Events
End point description:	
A clinically significant bleeding event is defined as any bleeding event of grade ≥ 2 per the modified World Health Organization (WHO) bleeding scale: • Grade 0 = no bleeding • Grade 1 = petechia or mucosal or retinal bleeding not requiring intervention • Grade 2 = melena, hematemesis, hematuria, hemoptysis • Grade 3 = bleeding required red cell transfusion • Grade 4 = retinal bleeding with visual impairment • Grade 5 = non-fatal cerebral bleeding • Grade 6 = fatal cerebral bleeding • Grade 7 = fatal non-cerebral bleeding. Bleeding events that continue for more than 7 days were counted as separate events every eighth day. Multiple events that arose from one organ system on one day were collapsed into one single event. Bleeding events with a start date between the first dose date and the last dose date of the test treatment period+7 days are included.	
End point type	Primary
End point timeframe:	
Test Treatment Period (Weeks 1-26)	

End point values	Placebo	Romiplostim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	167		
Units: events	116	178		

Statistical analyses

Statistical analysis title	Primary Analysis
Comparison groups	Placebo v Romiplostim
Number of subjects included in analysis	250
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.13 [1]
Method	Anderson-Gill model
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	1.05

Notes:

[1] - Anderson-Gill model using the model-based variance estimate and stratified by the randomization stratification factors

Secondary: Annualized Rate of Platelet Transfusion Events

End point title	Annualized Rate of Platelet Transfusion Events

End point description:

A discrete platelet transfusion is any number of platelet transfusions given within a 3-day period administered in order to intervene to treat a specific bleeding event or to treat severe thrombocytopenia where the platelet count was < 10 x 10^9/L. Transfusions administered more than 3 days apart were counted as separate events. Transfusion given in the absence of any bleeding, when the platelet count is > 10x10^9/L, was not counted as a platelet transfusion event. Events with start date between the first dose date and the last dose date of the test treatment period +7 days are included. Exposure adjusted event rate per 100 patient-years = (events / patient-years * 100). Patient Year = total patient years of exposure to study drug during the 26 weeks test treatment period.

End point type	Secondary

End point timeframe:

Test Treatment Period (Weeks 1-26)

End point values	Placebo	Romiplostim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	167		
Units: events per 100 patient-years				
number (confidence interval 95%)	1013.5 (905.2 to 1131.3)	748.9 (681.3 to 821.4)		

Statistical analyses

Statistical analysis title	Key Secondary Analysis
Comparison groups	Placebo v Romiplostim
Number of subjects included in analysis	250
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [2]
Method	Poisson regression model
Parameter estimate	Risk ratio (RR)
Point estimate	0.766
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.66
upper limit	0.88

Notes:

[2] - Poisson regression model with treatment and stratification factors as covariates.

Secondary: Annualized Rate of Overall Bleeding Events

End point title	Annualized Rate of Overall Bleeding Events

End point description:

A bleeding event is defined as any bleeding event (clinically significant and not clinically significant) reported during the test treatment period. Bleeding events that continued for more than 7 days were counted as separate events every eighth day. Multiple events that arose from one organ system on one day were collapsed into one single event. Bleeding events with start date between the first dose date and the last dose date of the test treatment period+7 days are included.
Exposure adjusted event rate per 100 patient-years = events / patient-year * 100).

End point type	Secondary

End point timeframe:

Test Treatment Period (Weeks 1-26)

End point values	Placebo	Romiplostim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	167		
Units: events per 100 patient-years				
number (confidence interval 95%)	3786.4 (3574.1 to 4008)	3459.9 (3312.8 to 3611.9)		

Statistical analyses

Statistical analysis title	Analysis of Overall Bleeding Events
Comparison groups	Placebo v Romiplostim
Number of subjects included in analysis	250
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.026 [3]
Method	Poisson regression model
Parameter estimate	Risk ratio (RR)
Point estimate	0.922
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.86
upper limit	0.99

Notes:

[3] - Poisson regression model with treatment and stratification factors as covariates.

Secondary: Annualized Rate of Total Platelet Transfusion Units

End point title	Annualized Rate of Total Platelet Transfusion Units

End point description:

A unit of platelets is defined as a single pack of pooled platelet-rich plasma comprised of 6 to 8

individual platelet concentrate packs (200 to 400 mL), a single pack of pooled buffy-coat concentrate, or 1 apheresis (single donor) concentrate. Exposure adjusted event rate per 100 patient-years = events / patient-years * 100.

End point type	Secondary

End point timeframe:

Test Treatment Period (Weeks 1-26)

End point values	Placebo	Romiplostim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	167		
Units: units per 100 patient-years				
number (confidence interval 95%)	3120.2 (2927.8 to 3322)	2221.8 (2104.2 to 2344.2)		

Statistical analyses

Statistical analysis title	Analysis of Total Platelet Transfusion Units
Comparison groups	Placebo v Romiplostim
Number of subjects included in analysis	250
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [4]
Method	Poisson regression model
Parameter estimate	Risk ratio (RR)
Point estimate	0.739
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	0.8

Notes:

[4] - Poisson regression model with treatment and stratification factors as covariates

Secondary: Number of Participants With Platelet Hematologic Improvement (HI-P)

End point title	Number of Participants With Platelet Hematologic Improvement (HI-P)

End point description:

Platelet hematologic improvement is defined by the international working group (IWG) as: an absolute increase in platelet count of ≥ 30 x 10^9/L for patients starting with a platelet count of ≥ 20 x 10^9/L or an increase in platelet count to ≥ 20 x 10^9/L and by at least 100% in a patient that started with a platelet count < 20 x 10^9/L. To account for any possible contribution from platelet transfusions, platelet counts within 3 days following administration of platelet transfusion were not counted towards the platelet hematologic improvement endpoint. If no platelet measurements were available on the weekly scheduled dose day, then that week was not counted towards the platelet hematologic improvement endpoint.

End point type	Secondary

End point timeframe:

Test Treatment Period (Weeks 1-26)

End point values	Placebo	Romiplostim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	167		
Units: participants				
number (not applicable)	3	61		

Statistical analyses

Statistical analysis title	Analysis of Platelet Hematologic Improvement
Comparison groups	Placebo v Romiplostim
Number of subjects included in analysis	250
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [5]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	15.6
Confidence interval	
level	95 %
sides	2-sided
lower limit	4.7
upper limit	51.8

Notes:

[5] - Cochran-Mantel-Haenszel test controlling for stratification factors.

Secondary: Exposure-adjusted Total Duration of Platelet Hematologic Improvement (HI-P) in the Absence of Platelet Transfusions

End point title	Exposure-adjusted Total Duration of Platelet Hematologic Improvement (HI-P) in the Absence of Platelet Transfusions

End point description:

Duration for participants who did not report HI-P during the period is 0. A platelet hematologic improvement (HI-P) is defined by an MDS IWG criteria as patients with a baseline platelet count of ≥ 20 x 10^9/L achieving an absolute increase of ≥ 30 x 10^9/L or increasing the platelet count to above 20 x 10^9/L and by at least 100% in patients with a baseline of < 20 x 10^9/L for at least 8 consecutive weeks. To account for any possible contribution from platelet transfusions, platelet counts within 3 days following administration of platelet transfusion were not counted towards the platelet hematologic improvement endpoint. If no platelet measurements were available on the weekly scheduled dose day, then that week was not counted towards the platelet hematologic improvement endpoint. The durations of HI-P are cumulative if more than one incidence occurred. Exposure adjusted event rate per 100 patient-weeks = total number of weeks / patient-weeks * 100.

End point type	Secondary

End point timeframe:

Test Treatment Period (Weeks 1-26)

End point values	Placebo	Romiplostim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	167		
Units: weeks per 100 patient-weeks				
number (confidence interval 95%)	2.57 (1.85 to 3.47)	35.02 (32.98 to 37.16)		

Statistical analyses

Statistical analysis title	Analysis of Duration of HI-P
Comparison groups	Placebo v Romiplostim
Number of subjects included in analysis	250
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.032 [6]
Method	Poisson regression model
Parameter estimate	Risk ratio (RR)
Point estimate	1.402
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.03
upper limit	1.91

Notes:

[6] - Poisson regression model with treatment and stratification factors as covariates

Secondary: Overall Survival

End point title	Overall Survival

End point description:

Overall survival time was calculated as the number of months from first dose of study drug to death or date of censoring. Subjects who were not reported as having died were censored. Overall survival was calculated using Kaplan-Meier methods.

End point type	Secondary

End point timeframe:

From date of first dose of study drug to the end of the long term follow-up; median observation time was 27.5 months.

End point values	Placebo	Romiplostim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	83	167		
Units: months				
median (confidence interval 95%)	35.7 (27.5 to 57.7)	32.3 (27.4 to 45.4)		

Statistical analyses

No statistical analyses for this end point

Secondary: Annualized Rate of Patient-reported Bleeding Events

End point title	Annualized Rate of Patient-reported Bleeding Events

End point description:

The number of bleeding events was obtained from the thrombocytopenia symptoms (Th-symptoms) survey. Patients reported spontaneous bleeding to have occurred 0, 1 or 2, 3 or 4, 5 or 6, or 7 or more times in the past week. The lower threshold of bleeding counts is used for conservative purposes (i.e., the "3" is used for the response option of "3 or 4 times"). Exposure adjusted event rate per 100 patient-years = number of events / patient-year * 100.

End point type	Secondary

End point timeframe:

Test Treatment Period (Weeks 1-26)

End point values	Placebo	Romiplostim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	82	162		
Units: events per 100 patient-years				
number (confidence interval 95%)	1995 (1840.5 to 2158.9)	1264 (1175.1 to 1357.7)		

Statistical analyses

Statistical analysis title	Analysis of Patient-Reported Bleeding Events
Comparison groups	Placebo v Romiplostim
Number of subjects included in analysis	244
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001 [7]
Method	Poisson regression model
Parameter estimate	Risk ratio (RR)
Point estimate	0.639
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	0.71

Notes:

[7] - Poisson regression model with treatment and stratification factors as covariates

Adverse events

Adverse events information

Timeframe for reporting adverse events:

58 weeks

Adverse event reporting additional description:

The safety analysis set consisted of 250 patients including 168 in the romiplostim group and 82 in the placebo group. One patient enrolled in the placebo group received 1 dose of romiplostim at week 4 of the extended treatment period. Results for this patient were analyzed as part of the romiplostim group in the Safety Analysis Set.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups

Reporting group title	Romiplostim
Reporting group description: -	
Reporting group title	Placebo

Reporting group description: -

Serious adverse events	Romiplostim	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	67 / 168 (39.88%)	22 / 82 (26.83%)	
number of deaths (all causes)	93	45	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma of colon			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Basal cell carcinoma			
subjects affected / exposed	0 / 168 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung neoplasm malignant			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myelofibrosis			

subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage			
subjects affected / exposed	0 / 168 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertensive crisis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Shock haemorrhagic			
subjects affected / exposed	0 / 168 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Thrombosis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 168 (1.19%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Fatigue			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General physical health deterioration			
subjects affected / exposed	0 / 168 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hernia			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Malaise			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Multi-organ failure			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pyrexia			
subjects affected / exposed	7 / 168 (4.17%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	1 / 7	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Vaginal haemorrhage			
subjects affected / exposed	0 / 168 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			

subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			
subjects affected / exposed	1 / 168 (0.60%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epistaxis			
subjects affected / exposed	4 / 168 (2.38%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 5	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Investigations			
Blast cell count increased			
subjects affected / exposed	0 / 168 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatic enzyme increased			
subjects affected / exposed	0 / 168 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myeloblast count increased			
subjects affected / exposed	2 / 168 (1.19%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	2 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oxygen saturation decreased			
subjects affected / exposed	0 / 168 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Head injury			
subjects affected / exposed	4 / 168 (2.38%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Joint dislocation			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Overdose			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Post procedural haemorrhage			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Procedural complication			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal compression fracture			
subjects affected / exposed	0 / 168 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Stoma site haemorrhage			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			

subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transfusion reaction			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ulna fracture			
subjects affected / exposed	0 / 168 (0.00%)	1 / 82 (1.22%)	
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	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 168 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Atrial fibrillation			
subjects affected / exposed	5 / 168 (2.98%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 5	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	0 / 168 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiogenic shock			
subjects affected / exposed	0 / 168 (0.00%)	1 / 82 (1.22%)	
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	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coronary artery stenosis			
subjects affected / exposed	0 / 168 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Myocardial infarction			
subjects affected / exposed	2 / 168 (1.19%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 2	0 / 0	
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 168 (0.00%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 2	
Dizziness			
subjects affected / exposed	2 / 168 (1.19%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Headache			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hydrocephalus			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lateral medullary syndrome			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subarachnoid haemorrhage			

subjects affected / exposed	0 / 168 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	2 / 168 (1.19%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	7 / 168 (4.17%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 7	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Aplastic anaemia			
subjects affected / exposed	0 / 168 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extramedullary haemopoiesis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	2 / 168 (1.19%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 5	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Iron deficiency anaemia			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			

subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenia			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancytopenia			
subjects affected / exposed	0 / 168 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Splenic infarction			
subjects affected / exposed	2 / 168 (1.19%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thrombocytopenia			
subjects affected / exposed	6 / 168 (3.57%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 6	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Abdominal pain upper			
subjects affected / exposed	0 / 168 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			

subjects affected / exposed	1 / 168 (0.60%)	2 / 82 (2.44%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastric ulcer			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	3 / 168 (1.79%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 4	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 1	
Gingival bleeding			
subjects affected / exposed	1 / 168 (0.60%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematemesis			
subjects affected / exposed	0 / 168 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Melaena			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mesenteric artery thrombosis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Mouth haemorrhage			
subjects affected / exposed	1 / 168 (0.60%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Acute hepatic failure			

subjects affected / exposed	0 / 168 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Hepatic cirrhosis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute prerenal failure			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Haematuria			
subjects affected / exposed	1 / 168 (0.60%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrolithiasis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Obstructive uropathy			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	2 / 168 (1.19%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 168 (0.60%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Osteosclerosis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Anal abscess			
subjects affected / exposed	0 / 168 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchitis			
subjects affected / exposed	2 / 168 (1.19%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Chronic sinusitis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Encephalitis			
subjects affected / exposed	0 / 168 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	2 / 168 (1.19%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia sepsis			
subjects affected / exposed	0 / 168 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
External ear cellulitis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			

subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis norovirus			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis viral			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gingivitis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower respiratory tract infection			
subjects affected / exposed	0 / 168 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neutropenic sepsis			
subjects affected / exposed	2 / 168 (1.19%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 2	0 / 0	
Pneumonia			
subjects affected / exposed	10 / 168 (5.95%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	1 / 13	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pneumonia viral			
subjects affected / exposed	0 / 168 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis			

subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory tract infection			
subjects affected / exposed	0 / 168 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	3 / 168 (1.79%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Viral pericarditis			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 168 (0.00%)	1 / 82 (1.22%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 168 (0.60%)	0 / 82 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Romiplostim	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	147 / 168 (87.50%)	73 / 82 (89.02%)	
Vascular disorders			
Capillary fragility			
subjects affected / exposed	0 / 168 (0.00%)	5 / 82 (6.10%)	
occurrences (all)	0	5	
Haematoma			
subjects affected / exposed	58 / 168 (34.52%)	34 / 82 (41.46%)	
occurrences (all)	319	169	
Haemorrhage			
subjects affected / exposed	24 / 168 (14.29%)	15 / 82 (18.29%)	
occurrences (all)	73	30	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	22 / 168 (13.10%)	7 / 82 (8.54%)	
occurrences (all)	25	9	
Fatigue			
subjects affected / exposed	24 / 168 (14.29%)	7 / 82 (8.54%)	
occurrences (all)	43	17	
Injection site bruising			
subjects affected / exposed	6 / 168 (3.57%)	6 / 82 (7.32%)	
occurrences (all)	15	11	
Injection site haematoma			
subjects affected / exposed	6 / 168 (3.57%)	6 / 82 (7.32%)	
occurrences (all)	13	8	
Oedema peripheral			
subjects affected / exposed	23 / 168 (13.69%)	6 / 82 (7.32%)	
occurrences (all)	25	8	
Pyrexia			
subjects affected / exposed	18 / 168 (10.71%)	12 / 82 (14.63%)	
occurrences (all)	28	18	
Vessel puncture site haematoma			

subjects affected / exposed	4 / 168 (2.38%)	5 / 82 (6.10%)	
occurrences (all)	4	6	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	25 / 168 (14.88%)	10 / 82 (12.20%)	
occurrences (all)	37	10	
Dyspnoea			
subjects affected / exposed	13 / 168 (7.74%)	4 / 82 (4.88%)	
occurrences (all)	16	5	
Epistaxis			
subjects affected / exposed	66 / 168 (39.29%)	32 / 82 (39.02%)	
occurrences (all)	188	179	
Oropharyngeal pain			
subjects affected / exposed	9 / 168 (5.36%)	4 / 82 (4.88%)	
occurrences (all)	10	5	
Psychiatric disorders			
Insomnia			
subjects affected / exposed	13 / 168 (7.74%)	2 / 82 (2.44%)	
occurrences (all)	13	2	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	41 / 168 (24.40%)	10 / 82 (12.20%)	
occurrences (all)	297	77	
Nervous system disorders			
Dizziness			
subjects affected / exposed	16 / 168 (9.52%)	6 / 82 (7.32%)	
occurrences (all)	20	6	
Headache			
subjects affected / exposed	29 / 168 (17.26%)	10 / 82 (12.20%)	
occurrences (all)	56	11	
Syncope			
subjects affected / exposed	0 / 168 (0.00%)	5 / 82 (6.10%)	
occurrences (all)	0	6	
Blood and lymphatic system disorders			
Anaemia			

subjects affected / exposed	16 / 168 (9.52%)	7 / 82 (8.54%)	
occurrences (all)	33	14	
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	9 / 168 (5.36%)	5 / 82 (6.10%)	
occurrences (all)	11	11	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	10 / 168 (5.95%)	5 / 82 (6.10%)	
occurrences (all)	12	5	
Constipation			
subjects affected / exposed	9 / 168 (5.36%)	6 / 82 (7.32%)	
occurrences (all)	10	6	
Diarrhoea			
subjects affected / exposed	24 / 168 (14.29%)	10 / 82 (12.20%)	
occurrences (all)	31	14	
Gingival bleeding			
subjects affected / exposed	33 / 168 (19.64%)	14 / 82 (17.07%)	
occurrences (all)	107	52	
Mouth haemorrhage			
subjects affected / exposed	21 / 168 (12.50%)	8 / 82 (9.76%)	
occurrences (all)	35	47	
Nausea			
subjects affected / exposed	27 / 168 (16.07%)	7 / 82 (8.54%)	
occurrences (all)	38	8	
Vomiting			
subjects affected / exposed	8 / 168 (4.76%)	5 / 82 (6.10%)	
occurrences (all)	10	6	
Skin and subcutaneous tissue disorders			
Blood blister			
subjects affected / exposed	25 / 168 (14.88%)	11 / 82 (13.41%)	
occurrences (all)	77	31	
Ecchymosis			
subjects affected / exposed	20 / 168 (11.90%)	8 / 82 (9.76%)	
occurrences (all)	37	32	
Petechiae			

subjects affected / exposed	42 / 168 (25.00%)	20 / 82 (24.39%)	
occurrences (all)	84	55	
Pruritus			
subjects affected / exposed	10 / 168 (5.95%)	6 / 82 (7.32%)	
occurrences (all)	10	6	
Rash			
subjects affected / exposed	12 / 168 (7.14%)	10 / 82 (12.20%)	
occurrences (all)	14	10	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	20 / 168 (11.90%)	3 / 82 (3.66%)	
occurrences (all)	30	4	
Back pain			
subjects affected / exposed	16 / 168 (9.52%)	6 / 82 (7.32%)	
occurrences (all)	17	8	
Bone pain			
subjects affected / exposed	9 / 168 (5.36%)	0 / 82 (0.00%)	
occurrences (all)	11	0	
Musculoskeletal pain			
subjects affected / exposed	14 / 168 (8.33%)	3 / 82 (3.66%)	
occurrences (all)	18	4	
Myalgia			
subjects affected / exposed	4 / 168 (2.38%)	5 / 82 (6.10%)	
occurrences (all)	4	5	
Pain in extremity			
subjects affected / exposed	17 / 168 (10.12%)	5 / 82 (6.10%)	
occurrences (all)	20	5	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	13 / 168 (7.74%)	7 / 82 (8.54%)	
occurrences (all)	19	9	
Oral herpes			
subjects affected / exposed	7 / 168 (4.17%)	5 / 82 (6.10%)	
occurrences (all)	12	5	
Upper respiratory tract infection			

subjects affected / exposed occurrences (all)	6 / 168 (3.57%) 6	6 / 82 (7.32%) 8	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	 17 / 168 (10.12%) 20	 2 / 82 (2.44%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 April 2008	• The main purpose of this amendment was to allow for the inclusion of subjects with a platelet count ≤ 50 x 10^9/L, with a history of bleeding (rather than a history of clinically significant bleeding). Revising this inclusion criterion was intended to enhance enrollment. • To ensure consistency among romiplostim MDS study protocols, the definition of disease progression was revised. Previously, disease progression was defined as an IPSS low or INT-1 risk score that increased to an intermediate-2 or higher risk. With this amendment, disease progression was newly defined as transformation to AML. • Other administrative and typographical errors were corrected including the revision of the informed consent form (ICF) (Platelet Function Addendum) to accurately reflect the requirements of the protocol regarding the times of sampling.
19 November 2008	• The original protocol inadvertently excluded subjects with a normal total bilirubin. The main purpose of this amendment was to allow for the inclusion of subjects with a normal total bilirubin (total bilirubin ≤ 2.0 × the laboratory normal range). • The eligibility criteria pertaining to written informed consent (IC) was revised to allow a subject's legally acceptable representative to sign the ICF. If legally acceptable representatives were not permitted to sign the ICF per local law, the ICF and patient information sheet were to be locally revised appropriately. • Data captured in the long term follow up (LTFU) were clarified to inform that subjects were requested to allow Sponsor continued access to medical records, so that information related to subjects' health condition may be obtained during the LTFU period. • Bone marrow biopsy with aspirate and cytogenetics could be sent to a central laboratory if a site's local laboratory cytogenetics certification does not meet ICH GCP requirements. • Clarification of dose adjustment rules: for subjects receiving 250 µg romiplostim or volume-matched placebo weekly, the dose of IP would be withheld any time the platelet count was > 450 x 10^9/L and then reinitiated once every 2 weeks at the next scheduled visit the platelet count was < 200 x 10^9/L; subjects who had a previous dose reduction could increase the dose of IP if their platelet count was < 50 x 10^9/L for 3 consecutive weeks, beginning on the fourth week after the platelet count first fell to < 50 x 10^9/L. • To ensure consistency among romiplostim MDS studies, if the subject's marrow was inaspirable, a cytogenetic analysis was performed on a peripheral blood sample. • Other administrative and typographical errors were corrected including the revision of the ICF to accurately reflect the purpose of the study, regions in which the study was conducted and to remove the reference to exploratory research and discontinuation of medications for ITP.

23 October 2009	• The definition of disease progression and transformation to AML was clarified. Disease progression to AML was now to be assessed per WHO guidelines requiring confirmation of marrow or peripheral blast cells ≥ 20% that exists in the absence of romiplostim (4 weeks off dosing) and other hematopoietic growth factors (2 weeks off dosing). A pathology report confirming other leukemias such as chloroma (granulocytic sarcoma, myeloid sarcoma) or leukemia cutis would also constitute disease progression to AML. • For the purpose of this study, the definition of transformation to AML was expanded to also include any subject that clinically required the initiation of antileukemic treatment based on physician judgment and clinical diagnosis. • Due to the new requirement for subjects to be removed from IP for 4 weeks to study the bone marrow, the interim washout period duration was revised from 2 to 4 weeks to 4 weeks. • The timing of entrance criteria was further clarified to provide investigative sites with more detailed instruction of when disease related assessments should take place relative to the screening period. • The platelet function testing sub-study was removed from the protocol as a result of the primary investigator who was leading the sub-study resigned from the investigative site and declined further study participation. • The consent form was removed as a protocol appendix and was now to be provided separately to investigative sites. The consent form was also updated to reflect changes in study procedures and the most current safety information.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported