



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 ($\geq 20 \times 10^9/L$ or $< 20 \times 10^9/L$) 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 \geq 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 $< 10 \times 10^9/L$. 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 $> 10 \times 10^9/L$, 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 $\geq 30 \times 10^9/L$ for patients starting with a platelet count of $\geq 20 \times 10^9/L$ or an increase in platelet count to $\geq 20 \times 10^9/L$ and by at least 100% in a patient that started with a platelet count $< 20 \times 10^9/L$. 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 $\geq 20 \times 10^9/L$ achieving an absolute increase of $\geq 30 \times 10^9/L$ or increasing the platelet count to above $20 \times 10^9/L$ and by at least 100% in patients with a baseline of $< 20 \times 10^9/L$ 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 occurrences (all) | 4 / 168 (2.38%) 4 | 5 / 82 (6.10%) 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 occurrences (all) | 16 / 168 (9.52%) 33 | 7 / 82 (8.54%) 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 | <ul style="list-style-type: none">• The main purpose of this amendment was to allow for the inclusion of subjects with a platelet count $\leq 50 \times 10^9/L$, 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 | <ul style="list-style-type: none">• 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 $\leq 2.0 \times$ 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 $> 450 \times 10^9/L$ and then reinitiated once every 2 weeks at the next scheduled visit the platelet count was $< 200 \times 10^9/L$; subjects who had a previous dose reduction could increase the dose of IP if their platelet count was $< 50 \times 10^9/L$ for 3 consecutive weeks, beginning on the fourth week after the platelet count first fell to $< 50 \times 10^9/L$.• 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 | <ul style="list-style-type: none"> • 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 $\geq 20\%$ 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