

**Clinical trial results:****A Single Arm, Open-label, Long-term Efficacy and Safety Study of Romiplostim in Thrombocytopenic Pediatric Subjects With Immune Thrombocytopenia (ITP)****Summary**

| | |
|--------------------------|-------------------------------------|
| EudraCT number | 2011-005019-96 |
| Trial protocol | CZ BE ES GB HU Outside EU/EEA PL FR |
| Global end of trial date | 15 August 2019 |

Results information

| | |
|--------------------------------|------------------|
| Result version number | v1 |
| This version publication date | 22 February 2020 |
| First version publication date | 22 February 2020 |

Trial information**Trial identification**

| | |
|-----------------------|----------|
| Sponsor protocol code | 20101221 |
|-----------------------|----------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02279173 |
| 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) | Yes |
| EMA paediatric investigation plan number(s) | EMA-000653-PIP01-09 |
| 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? | Yes |

Notes:

Results analysis stage

| | |
|--|----------------|
| Analysis stage | Final |
| Date of interim/final analysis | 15 August 2019 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 15 August 2019 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The primary objectives were as follows: - to describe the percentage of time that pediatric subjects with ITP have a platelet response in the first 6 months from the start of treatment with romiplostim - to evaluate the incidence of changes in bone marrow findings at year 1 or year 2 after initial exposure to romiplostim

Protection of trial subjects:

This study was conducted in accordance with the United States Food and Drug Administration (FDA) and International Council for Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines. The protocol, informed consent, and all other subject information and/or recruitment materials were submitted to the Independent Ethics Committee (IEC) or Institutional Review Board (IRB) of each study center for approval. The investigator or a designee was to obtain written informed consent from their subjects or legally acceptable representatives after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol-specific screening procedures were conducted or investigational product was administered.

Background therapy: -

Evidence for comparator: -

| | |
|---|------------------|
| Actual start date of recruitment | 10 December 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Australia: 5 |
| Country: Number of subjects enrolled | Belgium: 18 |
| Country: Number of subjects enrolled | Brazil: 5 |
| Country: Number of subjects enrolled | Canada: 9 |
| Country: Number of subjects enrolled | Czech Republic: 11 |
| Country: Number of subjects enrolled | France: 4 |
| Country: Number of subjects enrolled | Hungary: 4 |
| Country: Number of subjects enrolled | Israel: 20 |
| Country: Number of subjects enrolled | Mexico: 2 |
| Country: Number of subjects enrolled | Poland: 5 |
| Country: Number of subjects enrolled | Russian Federation: 41 |
| Country: Number of subjects enrolled | South Africa: 8 |
| Country: Number of subjects enrolled | Spain: 12 |
| Country: Number of subjects enrolled | Switzerland: 3 |
| Country: Number of subjects enrolled | Turkey: 8 |

| | |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | United Kingdom: 14 |
| Country: Number of subjects enrolled | United States: 34 |
| Worldwide total number of subjects | 203 |
| EEA total number of subjects | 68 |

Notes:

Subjects enrolled per age group

| | |
|---|-----|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 1 |
| Children (2-11 years) | 129 |
| Adolescents (12-17 years) | 73 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

Children with immune thrombocytopenic purpura (ITP) and platelet counts $\leq 30 \times 10^9/L$ or uncontrolled bleeding were enrolled from December 2014 to August 2016 at 66 centers in 16 countries worldwide, including Eastern Europe (44%), Western Europe (25%), and US/Canada (21%).

Pre-assignment

Screening details:

All participants were assigned to receive weekly romiplostim. A subset of participants enrolled under a protocol supplement in the European Union (EU), Switzerland, and Turkey were enrolled into the following 2 cohorts: • bone marrow biopsy and aspirate at baseline and year 1 • bone marrow biopsy and aspirate at baseline and year 2

Period 1

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

Arms

| | |
|-----------|-------------|
| Arm title | Romiplostim |
|-----------|-------------|

Arm description:

Participants received romiplostim administered weekly by subcutaneous injection for up to 3 years. The starting dose was 1 $\mu\text{g}/\text{kg}$ titrated in 1 $\mu\text{g}/\text{kg}$ increments up to a maximum of 10 $\mu\text{g}/\text{kg}$ to reach a target platelet count $\geq 50 \times 10^9/L$.

| | |
|--|------------------------|
| Arm type | Experimental |
| Investigational medicinal product name | Romiplostim |
| Investigational medicinal product code | AMG 531 |
| Other name | NPLATE |
| Pharmaceutical forms | Solution for injection |
| Routes of administration | Subcutaneous use |

Dosage and administration details:

Romiplostim subcutaneous weekly injection

| Number of subjects in period 1 | Romiplostim |
|------------------------------------|-------------------|
| Started | 203 |
| Received Treatment | 203 |
| Enrolled Under Protocol Supplement | 79 ^[1] |
| Completed | 109 |
| Not completed | 94 |
| Consent withdrawn by subject | 20 |
| Decision by Sponsor | 4 |
| Lost to follow-up | 3 |
| Protocol-specified Criteria | 67 |

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.

Justification: A subset of 79 participants were enrolled under the EU Protocol Supplement.

Baseline characteristics

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Romiplostim |
|-----------------------|-------------|

Reporting group description:

Participants received romiplostim administered weekly by subcutaneous injection for up to 3 years. The starting dose was 1 µg/kg titrated in 1 µg/kg increments up to a maximum of 10 µg/kg to reach a target platelet count $\geq 50 \times 10^9/L$.

| Reporting group values | Romiplostim | Total | |
|---|--------------|-------|--|
| Number of subjects | 203 | 203 | |
| Age Categorical | | | |
| Units: participants | | | |
| ≥ 1 to < 6 years | 49 | 49 | |
| ≥ 6 to < 12 years | 81 | 81 | |
| ≥ 12 to < 18 years | 73 | 73 | |
| Age Continuous | | | |
| Units: years | | | |
| median | 10.0 | | |
| full range (min-max) | 1 to 17 | - | |
| Sex: Female, Male | | | |
| Units: participants | | | |
| Female | 103 | 103 | |
| Male | 100 | 100 | |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 4 | 4 | |
| Asian | 12 | 12 | |
| Black or African American | 11 | 11 | |
| Multiple | 1 | 1 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Other | 11 | 11 | |
| White | 164 | 164 | |
| Splenectomy Done | | | |
| Units: Subjects | | | |
| Yes | 10 | 10 | |
| No | 193 | 193 | |
| Years Since ITP Diagnosis | | | |
| Units: years | | | |
| median | 1.75 | | |
| full range (min-max) | 0.5 to 13.8 | - | |
| Age at ITP Diagnosis | | | |
| Units: years | | | |
| median | 5.97 | | |
| full range (min-max) | 0.6 to 17.3 | - | |
| Platelet Count | | | |
| Units: 10 cells/L | | | |
| median | 14.00 | | |
| full range (min-max) | 1.5 to 265.0 | - | |

| | | | |
|--------------------------------|--------|---|--|
| Number of Prior ITP Treatments | | | |
| Units: prior ITP treatments | | | |
| median | 2.0 | | |
| full range (min-max) | 1 to 7 | - | |

Subject analysis sets

| | |
|----------------------------|--------------------|
| Subject analysis set title | Cohort 1 |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants enrolled under the protocol supplement in the EU, Switzerland, or Turkey received weekly romiplostim for 3 years and had a bone marrow biopsy at baseline and year 1.

| | |
|----------------------------|--------------------|
| Subject analysis set title | Cohort 2 |
| Subject analysis set type | Sub-group analysis |

Subject analysis set description:

Participants enrolled under the protocol supplement in the EU, Switzerland, or Turkey received weekly romiplostim for 3 years and had a bone marrow biopsy at baseline and year 2.

| Reporting group values | Cohort 1 | Cohort 2 | |
|---|-------------|-------------|--|
| Number of subjects | 30 | 49 | |
| Age Categorical | | | |
| Units: participants | | | |
| ≥ 1 to < 6 years | 7 | 14 | |
| ≥ 6 to < 12 years | 13 | 13 | |
| ≥ 12 to < 18 years | 10 | 22 | |
| Age Continuous | | | |
| Units: years | | | |
| median | 10.5 | 10.0 | |
| full range (min-max) | 2 to 16 | 1 to 17 | |
| Sex: Female, Male | | | |
| Units: participants | | | |
| Female | 15 | 27 | |
| Male | 15 | 22 | |
| Race/Ethnicity, Customized | | | |
| Units: Subjects | | | |
| American Indian or Alaska Native | 0 | 0 | |
| Asian | 2 | 4 | |
| Black or African American | 0 | 1 | |
| Multiple | 0 | 0 | |
| Native Hawaiian or Other Pacific Islander | 0 | 0 | |
| Other | 2 | 0 | |
| White | 26 | 44 | |
| Splenectomy Done | | | |
| Units: Subjects | | | |
| Yes | 1 | 2 | |
| No | 29 | 47 | |
| Years Since ITP Diagnosis | | | |
| Units: years | | | |
| median | 3.08 | 1.14 | |
| full range (min-max) | 0.6 to 11.0 | 0.5 to 11.2 | |
| Age at ITP Diagnosis | | | |

| | | | |
|---|---------------------|---------------------|--|
| Units: years median full range (min-max) | 5.38 0.6 to 16.2 | 7.63 1.3 to 16.0 | |
| Platelet Count Units: 10 cells/L median full range (min-max) | | | |
| Number of Prior ITP Treatments Units: prior ITP treatments median full range (min-max) | 2.0 1 to 5 | 2.0 1 to 7 | |

End points

End points reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | Romiplostim |
|-----------------------|-------------|

Reporting group description:

Participants received romiplostim administered weekly by subcutaneous injection for up to 3 years. The starting dose was 1 µg/kg titrated in 1 µg/kg increments up to a maximum of 10 µg/kg to reach a target platelet count $\geq 50 \times 10/L$.

| | |
|----------------------------|----------|
| Subject analysis set title | Cohort 1 |
|----------------------------|----------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

Participants enrolled under the protocol supplement in the EU, Switzerland, or Turkey received weekly romiplostim for 3 years and had a bone marrow biopsy at baseline and year 1.

| | |
|----------------------------|----------|
| Subject analysis set title | Cohort 2 |
|----------------------------|----------|

| | |
|---------------------------|--------------------|
| Subject analysis set type | Sub-group analysis |
|---------------------------|--------------------|

Subject analysis set description:

Participants enrolled under the protocol supplement in the EU, Switzerland, or Turkey received weekly romiplostim for 3 years and had a bone marrow biopsy at baseline and year 2.

Primary: Percentage of Time with a Platelet Response During the First 6 Months of Treatment

| | |
|-----------------|---|
| End point title | Percentage of Time with a Platelet Response During the First 6 Months of Treatment ^[1] |
|-----------------|---|

End point description:

Platelet response was defined as a platelet count of $\geq 50 \times 10/L$ with no rescue medication use for ITP in the past 4 weeks. Monthly platelet response was calculated based on the median platelet count during each month. For each participant, the percentage of time with platelet response during the first 6 months was calculated as the number of months a platelet response was observed divided by the total number of months response was assessed. The efficacy analysis set included all enrolled participants who received at least 1 dose of romiplostim.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Week 2 to Month 6, platelet response was assessed every week.

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Formal hypothesis testing was not performed for this study. The statistical analysis in this open-label study was descriptive in nature.

| End point values | Romiplostim | | | |
|---------------------------------------|------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 203 | | | |
| Units: percentage of time | | | | |
| median (inter-quartile range (Q1-Q3)) | 50.00 (16.67 to 83.33) | | | |

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Developed Collagen after Exposure to Romiplostim

| | |
|-----------------|--|
| End point title | Percentage of Participants Who Developed Collagen after Exposure to Romiplostim ^[2] |
|-----------------|--|

End point description:

The percentage of participants who developed collagen as evidenced by trichrome staining, defined as a Grade 4 on the modified Bauermeister grading scale: Grade 0: No reticulin fibers demonstrable Grade 1: Occasional fine individual fibers and foci of a fine fiber network Grade 2: Fine fiber network throughout most of the section; no coarse fibers Grade 3: Diffuse fiber network with scattered thick coarse fibers but no mature collagen (negative to trichrome staining) Grade 4: Diffuse, often course fiber network with areas of collagenization (positive trichrome staining) The bone marrow analysis set includes participants who received at least 1 dose of romiplostim, who were recruited within the protocol supplement for the EU, Switzerland and Turkey and who had at least 1 bone marrow biopsy during the study after initiation of study treatment. Participants with available core biopsy results are included in the analysis.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Year 1 (Cohort 1) and year 2 (Cohort 2)

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Formal hypothesis testing was not performed for this study. The statistical analysis in this open-label study was descriptive in nature.

| End point values | Cohort 1 | Cohort 2 | | |
|-----------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 27 | 36 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 0.0 (0.0 to 12.8) | 0.0 (0.0 to 9.7) | | |

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants with Increased Modified Bauermeister Grade

| | |
|-----------------|--|
| End point title | Percentage of Participants with Increased Modified Bauermeister Grade ^[3] |
|-----------------|--|

End point description:

The percentage of participants with an increased modified Bauermeister grade defined as an increase by ≥ 2 severity grades or an increase to grade 4 (i.e., grade 0 to 2-4, grade 1 to 3-4, grade 2 to 4, or grade 3 to 4 over baseline). The modified Bauermeister grading scale: Grade 0: No reticulin fibers demonstrable Grade 1: Occasional fine individual fibers and foci of a fine fiber network Grade 2: Fine fiber network throughout most of the section; no coarse fibers Grade 3: Diffuse fiber network with scattered thick coarse fibers but no mature collagen (negative to trichrome staining) Grade 4: Diffuse, often course fiber network with areas of collagenization (positive trichrome staining) Participants in the bone marrow analysis set with available core biopsy results are included in the analysis. Participants without an evaluable baseline result were assumed to have a baseline modified Bauermeister score of 0.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline, year 1 (Cohort 1) and year 2 (Cohort 2)

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Formal hypothesis testing was not performed for this study. The statistical analysis in this open-label study was descriptive in nature.

| End point values | Cohort 1 | Cohort 2 | | |
|-----------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 27 | 36 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 3.7 (0.1 to 19.0) | 0.0 (0.0 to 9.7) | | |

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Participants Who Developed Bone Marrow Abnormalities

| | |
|-----------------|---|
| End point title | Percentage of Participants Who Developed Bone Marrow Abnormalities ^[4] |
|-----------------|---|

End point description:

The percentage of participants with bone marrow abnormalities (eg, myelodysplastic syndrome, monosomy 7) based on analysis of bone marrow biopsy and aspirate samples using cytogenetics and fluorescence in situ hybridization. Participants in the bone marrow analysis set with an on-study bone marrow abnormality assessment are included in the analysis.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Year 1 (Cohort 1) and year 2 (Cohort 2)

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: Formal hypothesis testing was not performed for this study. The statistical analysis in this open-label study was descriptive in nature.

| End point values | Cohort 1 | Cohort 2 | | |
|-----------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 27 | 31 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 0.0 (0.0 to 12.8) | 0.0 (0.0 to 11.2) | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Time With a Platelet Response During the Overall Treatment Period

| | |
|-----------------|---|
| End point title | Percentage of Time With a Platelet Response During the Overall Treatment Period |
|-----------------|---|

End point description:

Platelet response was defined as a platelet count of $\geq 50 \times 10^9$ cells/L with no rescue medication use in the past 4 weeks. Monthly platelet response was calculated based on the median platelet count during each month. For each participant, the percentage of time with platelet response was calculated as the number of months a platelet response was observed divided by the total number of months response was assessed. The efficacy analysis set was used for this analysis.

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

End point timeframe:

From week 2 to the end of the treatment period, 36 months

| | | | | |
|---------------------------------------|------------------------|--|--|--|
| End point values | Romiplostim | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 203 | | | |
| Units: percentage of time | | | | |
| median (inter-quartile range (Q1-Q3)) | 78.21 (26.67 to 90.39) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Time With an Increase in Platelet Count $\geq 20 \times 10$ Cells/L Above Baseline

| | |
|-----------------|--|
| End point title | Percentage of Time With an Increase in Platelet Count $\geq 20 \times 10$ Cells/L Above Baseline |
|-----------------|--|

End point description:

The percentage of time with an increase in platelet count $\geq 20 \times 10$ cells/L above baseline from week 2 until the end of the treatment period without rescue medication use within the past 4 weeks. For each participant, the percentage of time with an increase in platelet count $\geq 20 \times 10$ cells/L above baseline was calculated as the number of months the median platelet count was $\geq 20 \times 10$ cells/L above baseline divided by the total number of months assessed. The efficacy analysis set was used for this analysis.

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

End point timeframe:

Baseline and from week 2 to month 36

| | | | | |
|---------------------------------------|------------------------|--|--|--|
| End point values | Romiplostim | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 203 | | | |
| Units: percentage of time | | | | |
| median (inter-quartile range (Q1-Q3)) | 80.13 (39.13 to 92.31) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Reporting Use of Rescue Medications for ITP During the Treatment Period

| | |
|-----------------|--|
| End point title | Number of Participants Reporting Use of Rescue Medications for |
|-----------------|--|

End point description:

Rescue medication is defined as any medication or transfusion, other than romiplostim and excluded medications, that is administered after enrollment to the participant with the intent of raising platelet counts or to prevent bleeding and includes concomitant medications for ITP in which the dose and/or schedule was increased. Permitted rescue medications included the following: • corticosteroids • platelet transfusions • Intravenous immunoglobulin (IVIG) • azathioprine • anti-D immunoglobulin • danazol The efficacy analysis set was used for this analysis.

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

End point timeframe:

From first dose of romiplostim to the end of the treatment period, 36 months

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | Romiplostim | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 203 | | | |
| Units: participants | 60 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Who Developed Anti-Romiplostim or Anti-Thrombopoietin Neutralizing Antibodies

| | |
|-----------------|--|
| End point title | Number of Participants Who Developed Anti-Romiplostim or Anti-Thrombopoietin Neutralizing Antibodies |
|-----------------|--|

End point description:

Blood samples were first tested for the presence of binding antibodies to romiplostim or the peptide portion of romiplostim, and to endogenous thrombopoietin (eTPO). Samples testing positive for binding antibodies were then tested for neutralizing antibodies by assessing their ability to neutralize romiplostim and/or eTPO in a cell-based bioassay. Participants who developed neutralizing antibodies are those who had a postbaseline positive result with a negative or no result at baseline. Transient is defined as a negative result at the participant's last time point tested within the study period. Participants who received at least 1 dose of romiplostim and with a post-baseline antibody result are included in the analysis.

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

End point timeframe:

Week 12, week 52 and every 24 weeks thereafter up to month 36

| | | | | |
|--|-----------------|--|--|--|
| End point values | Romiplostim | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 203 | | | |
| Units: participants | | | | |
| Anti-romiplostim neutralizing antibodies | 7 | | | |
| Transient anti-romiplostim neutralizing antibodies | 4 | | | |
| Anti-eTPO neutralizing antibodies | 1 | | | |

| | | | | |
|---|---|--|--|--|
| Transient anti-eTPO neutralizing antibodies | 1 | | | |
|---|---|--|--|--|

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Adverse Events

| | |
|-----------------|--|
| End point title | Number of Participants with Adverse Events |
|-----------------|--|

End point description:

An adverse event (AE) was defined as any untoward medical occurrence in a clinical trial participant, which does not necessarily have a causal relationship with study treatment. A serious adverse event was defined as an AE that met at least 1 of the following criteria: • fatal • life threatening • required in-patient hospitalization or prolongation of existing hospitalization • resulted in persistent or significant disability/incapacity • congenital anomaly/birth defect • other medically important serious event Adverse events were graded for severity according to the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 grading scale, where Grade 1 = mild AE; Grade 2 = moderate AE; Grade 3 = severe AE; Grade 4 = life-threatening or disabling; Grade 5 = death related to AE. Participants who received at least 1 dose of romiplostim are included in the analysis.

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

End point timeframe:

From first dose of study drug to the end of treatment, up to 36 months.

| End point values | Romiplostim | | | |
|---|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 203 | | | |
| Units: participants | | | | |
| Any adverse event (AE) | 193 | | | |
| Serious adverse events (SAE) | 60 | | | |
| AEs leading to discontinuation of romiplostim | 15 | | | |
| Adverse event Grade \geq 3 | 66 | | | |
| Adverse event Grade \geq 4 | 19 | | | |
| Adverse event Grade \geq 5 | 0 | | | |
| Treatment-related adverse events (TRAE) | 56 | | | |
| Treatment-related serious adverse events | 8 | | | |
| TRAEs leading to discontinuation of romiplostim | 8 | | | |
| Treatment-related adverse events Grade \geq 3 | 8 | | | |
| Treatment-related adverse events Grade \geq 4 | 0 | | | |
| Treatment-related adverse events Grade \geq 5 | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who Developed Increased Reticulin

| | |
|-----------------|--|
| End point title | Percentage of Participants who Developed Increased Reticulin |
|-----------------|--|

End point description:

The percentage of participants with increased reticulin as evidenced by silver staining and defined as any increase from baseline in the modified Bauermeister grade: Grade 0: No reticulin fibers demonstrable Grade 1: Occasional fine individual fibers and foci of a fine fiber network Grade 2: Fine fiber network throughout most of the section; no coarse fibers Grade 3: Diffuse fiber network with scattered thick coarse fibers but no mature collagen (negative to trichrome staining) Grade 4: Diffuse, often coarse fiber network with areas of collagenization (positive trichrome staining) Participants in the bone marrow analysis set with available core biopsy results are included in the analysis. Participants without an evaluable baseline result were assumed to have a baseline modified Bauermeister score of 0.

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

End point timeframe:

Baseline, year 1 (Cohort 1) and year 2 (Cohort 2)

| End point values | Cohort 1 | Cohort 2 | | |
|-----------------------------------|----------------------|----------------------|--|--|
| Subject group type | Subject analysis set | Subject analysis set | | |
| Number of subjects analysed | 27 | 36 | | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 18.5 (6.3 to 38.1) | 47.2 (30.4 to 64.5) | | |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From first dose of study drug to the end of treatment, up to 36 months.

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

Dictionary used

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

| | |
|--------------------|------|
| Dictionary version | 22.0 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|-------------|
| Reporting group title | ROMIPLOSTIM |
|-----------------------|-------------|

Reporting group description:

Participants received romiplostim administered weekly by subcutaneous injection for up to 3 years. The starting dose was 1 µg/kg titrated in 1 µg/kg increments up to a maximum of 10 µg/kg to reach a target platelet count $\geq 50 \times 10^9/L$.

| Serious adverse events | ROMIPLOSTIM | | |
|---|-------------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 60 / 203 (29.56%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | | | |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| B-cell lymphoma | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vascular disorders | | | |
| Haemorrhage | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Reproductive system and breast disorders | | | |
| Gynaecomastia | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Menorrhagia | | | |

| | | | |
|--|------------------|--|--|
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metrorrhagia | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Polymenorrhoea | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Varicocele | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Epistaxis | | | |
| subjects affected / exposed | 12 / 203 (5.91%) | | |
| occurrences causally related to treatment / all | 0 / 17 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Interstitial lung disease | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Status asthmaticus | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Psychiatric disorders | | | |
| Suicidal ideation | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|------------------|--|--|
| Investigations | | | |
| Arthroscopy | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood urine present | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Neutralising antibodies positive | | | |
| subjects affected / exposed | 4 / 203 (1.97%) | | |
| occurrences causally related to treatment / all | 4 / 4 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Platelet count decreased | | | |
| subjects affected / exposed | 10 / 203 (4.93%) | | |
| occurrences causally related to treatment / all | 0 / 11 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Head injury | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Post procedural haemorrhage | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Road traffic accident | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Cardiac disorders | | | |
| Supraventricular tachycardia | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 2 / 203 (0.99%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Presyncope | | | |
| subjects affected / exposed | 2 / 203 (0.99%) | | |
| occurrences causally related to treatment / all | 1 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Blood and lymphatic system disorders | | | |
| Anaemia | | | |
| subjects affected / exposed | 2 / 203 (0.99%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Evans syndrome | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhagic disorder | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Immune thrombocytopenic purpura | | | |
| subjects affected / exposed | 3 / 203 (1.48%) | | |
| occurrences causally related to treatment / all | 0 / 3 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lymphadenitis | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombocytopenia | | | |
| subjects affected / exposed | 4 / 203 (1.97%) | | |
| occurrences causally related to treatment / all | 0 / 20 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Thrombocytopenic purpura | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastrointestinal disorders | | | |
| Abdominal pain | | | |
| subjects affected / exposed | 2 / 203 (0.99%) | | |
| occurrences causally related to treatment / all | 2 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gingival bleeding | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haematemesis | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mouth haemorrhage | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Tooth impacted | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Skin and subcutaneous tissue disorders | | | |

| | | | |
|---|-----------------|--|--|
| Ecchymosis | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Haemorrhage subcutaneous | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Petechiae | | | |
| subjects affected / exposed | 2 / 203 (0.99%) | | |
| occurrences causally related to treatment / all | 0 / 5 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Purpura | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Renal and urinary disorders | | | |
| Haematuria | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Lupus nephritis | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Haemarthrosis | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Mixed connective tissue disease | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

| | | | |
|---|-----------------|--|--|
| Systemic lupus erythematosus subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Infections and infestations | | | |
| Appendicitis | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Cytomegalovirus infection | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Gastroenteritis rotavirus | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Influenza | | | |
| subjects affected / exposed | 2 / 203 (0.99%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Otitis externa | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Otitis media acute | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Peritonsillar abscess | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pilonidal cyst | | | |

| | | | |
|---|-----------------|--|--|
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Staphylococcal abscess | | | |
| subjects affected / exposed | 1 / 203 (0.49%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

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

| Non-serious adverse events | ROMIPLOSTIM | | |
|---|--------------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 183 / 203 (90.15%) | | |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 40 / 203 (19.70%) | | |
| occurrences (all) | 365 | | |
| Fall | | | |
| subjects affected / exposed | 13 / 203 (6.40%) | | |
| occurrences (all) | 15 | | |
| Skin laceration | | | |
| subjects affected / exposed | 12 / 203 (5.91%) | | |
| occurrences (all) | 13 | | |
| Limb injury | | | |
| subjects affected / exposed | 11 / 203 (5.42%) | | |
| occurrences (all) | 14 | | |
| Vascular disorders | | | |
| Haematoma | | | |
| subjects affected / exposed | 42 / 203 (20.69%) | | |
| occurrences (all) | 164 | | |
| Nervous system disorders | | | |

| | | | |
|--|---|--|--|
| Dizziness subjects affected / exposed occurrences (all) | 14 / 203 (6.90%) 19 | | |
| Headache subjects affected / exposed occurrences (all) | 78 / 203 (38.42%) 334 | | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 13 / 203 (6.40%) 24 | | |
| General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) | 19 / 203 (9.36%) 25 65 / 203 (32.02%) 143 | | |
| Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all) | 15 / 203 (7.39%) 21 | | |
| Immune system disorders Hypersensitivity subjects affected / exposed occurrences (all) | 12 / 203 (5.91%) 16 | | |
| Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Gingival bleeding | 29 / 203 (14.29%) 45 39 / 203 (19.21%) 65 38 / 203 (18.72%) 94 | | |

| | | | |
|--|--------------------------|--|--|
| subjects affected / exposed occurrences (all) | 21 / 203 (10.34%) 29 | | |
| Mouth haemorrhage subjects affected / exposed occurrences (all) | 16 / 203 (7.88%) 29 | | |
| Nausea subjects affected / exposed occurrences (all) | 37 / 203 (18.23%) 66 | | |
| Vomiting subjects affected / exposed occurrences (all) | 47 / 203 (23.15%) 89 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 52 / 203 (25.62%) 125 | | |
| Epistaxis subjects affected / exposed occurrences (all) | 77 / 203 (37.93%) 319 | | |
| Nasal congestion subjects affected / exposed occurrences (all) | 18 / 203 (8.87%) 30 | | |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 37 / 203 (18.23%) 73 | | |
| Rhinorrhoea subjects affected / exposed occurrences (all) | 27 / 203 (13.30%) 46 | | |
| Skin and subcutaneous tissue disorders | | | |
| Ecchymosis subjects affected / exposed occurrences (all) | 19 / 203 (9.36%) 55 | | |
| Petechiae subjects affected / exposed occurrences (all) | 48 / 203 (23.65%) 192 | | |
| Rash | | | |

| | | | |
|--|-------------------------|--|--|
| subjects affected / exposed occurrences (all) | 27 / 203 (13.30%) 33 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Arthralgia | | | |
| subjects affected / exposed | 23 / 203 (11.33%) | | |
| occurrences (all) | 35 | | |
| Pain in extremity | | | |
| subjects affected / exposed | 22 / 203 (10.84%) | | |
| occurrences (all) | 39 | | |
| Infections and infestations | | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 13 / 203 (6.40%) | | |
| occurrences (all) | 15 | | |
| Ear infection | | | |
| subjects affected / exposed | 15 / 203 (7.39%) | | |
| occurrences (all) | 18 | | |
| Gastroenteritis | | | |
| subjects affected / exposed | 19 / 203 (9.36%) | | |
| occurrences (all) | 25 | | |
| Influenza | | | |
| subjects affected / exposed | 18 / 203 (8.87%) | | |
| occurrences (all) | 26 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 75 / 203 (36.95%) | | |
| occurrences (all) | 191 | | |
| Pharyngitis | | | |
| subjects affected / exposed | 32 / 203 (15.76%) | | |
| occurrences (all) | 56 | | |
| Rhinitis | | | |
| subjects affected / exposed | 40 / 203 (19.70%) | | |
| occurrences (all) | 69 | | |
| Tonsillitis | | | |
| subjects affected / exposed | 15 / 203 (7.39%) | | |
| occurrences (all) | 16 | | |
| Upper respiratory tract infection | | | |

| | | | |
|-----------------------------|-------------------|--|--|
| subjects affected / exposed | 39 / 203 (19.21%) | | |
| occurrences (all) | 107 | | |
| Viral infection | | | |
| subjects affected / exposed | 21 / 203 (10.34%) | | |
| occurrences (all) | 54 | | |
| Sinusitis | | | |
| subjects affected / exposed | 11 / 203 (5.42%) | | |
| occurrences (all) | 14 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|----------------|---|
| 15 July 2014 | As a result of regulatory reviews, additional routine monitoring has been added to the protocol. This amendment includes the following changes: - to update the inclusion criteria to include hematologic, renal, and liver criteria - to add pregnancy monitoring as applicable every 12 weeks and at the EOT visit |
| 15 August 2014 | - Exclusion criteria were modified to allow prior use of eltrombopag within 4 weeks of enrollment. - A correction was made to the dose adjustment rules in the Table 1. - Removal of reticulocytes from the laboratory specimens. - "Protocol specified criteria" were added to Section 8.2.1 Reasons for Removal From Treatment and Section 8.2.2 Reasons for Removal From Study. - Serious adverse event completion instructions (Appendix A) for faxed forms were updated. |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported