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)	EMEA-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 ≤ 30×10/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 µg/kg titrated in 1 µg/kg increments up to a maximum of 10 µg/kg to reach a target platelet count ≥ 50 x 10/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 ≥ 50 x 10/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	5.38	7.63	
full range (min-max)	0.6 to 16.2	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	2.0	2.0	
full range (min-max)	1 to 5	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 ≥ 50 x 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 ≥ 50 x 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 ≥ 50 x 10 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 ≥ 20 x 10 Cells/L Above Baseline

End point title	Percentage of Time With an Increase in Platelet Count ≥ 20 x 10 Cells/L Above Baseline

End point description:

The percentage of time with an increase in platelet count ≥ 20 x 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 ≥ 20 x10 cells/L above baseline was calculated as the number of months the median platelet count was ≥ 20 x10 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

	ITP During the Treatment Period

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 ≥ 3	66			
Adverse event Grade ≥ 4	19			
Adverse event Grade ≥ 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 ≥ 3	8			
Treatment-related adverse events Grade ≥ 4	0			
Treatment-related adverse events Grade ≥ 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 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	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 ≥ 50 x 10/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) Headache subjects affected / exposed occurrences (all)	 14 / 203 (6.90%) 19 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	21 / 203 (10.34%)		
occurrences (all)	29		
Mouth haemorrhage			
subjects affected / exposed	16 / 203 (7.88%)		
occurrences (all)	29		
Nausea			
subjects affected / exposed	37 / 203 (18.23%)		
occurrences (all)	66		
Vomiting			
subjects affected / exposed	47 / 203 (23.15%)		
occurrences (all)	89		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	52 / 203 (25.62%)		
occurrences (all)	125		
Epistaxis			
subjects affected / exposed	77 / 203 (37.93%)		
occurrences (all)	319		
Nasal congestion			
subjects affected / exposed	18 / 203 (8.87%)		
occurrences (all)	30		
Oropharyngeal pain			
subjects affected / exposed	37 / 203 (18.23%)		
occurrences (all)	73		
Rhinorrhoea			
subjects affected / exposed	27 / 203 (13.30%)		
occurrences (all)	46		
Skin and subcutaneous tissue disorders			
Ecchymosis			
subjects affected / exposed	19 / 203 (9.36%)		
occurrences (all)	55		
Petechiae			
subjects affected / exposed	48 / 203 (23.65%)		
occurrences (all)	192		
Rash			

subjects affected / exposed	27 / 203 (13.30%)		
occurrences (all)	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