



Clinical trial results:

An Open-label Study Evaluating the Safety and Efficacy of Long-term Dosing of Romiplostim in Thrombocytopenic Pediatric Subjects With Immune (Idiopathic) Thrombocytopenia Purpura (ITP)

Summary

EudraCT number	2009-016203-32
Trial protocol	ES Outside EU/EEA
Global end of trial date	12 January 2017

Results information

Result version number	v1 (current)
This version publication date	16 July 2017
First version publication date	16 July 2017

Trial information

Trial identification

Sponsor protocol code	20090340
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01071954
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	12 January 2017
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	12 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the safety of romiplostim as a long-term treatment in pediatric thrombocytopenic subjects with ITP.

Protection of trial subjects:

This study was conducted in accordance with International Council on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines, United States Food and Drug Administration (FDA) GCP regulations/guidelines, and the GCP regulations/guidelines to all regions where the study was conducted. The investigator submitted the protocol, informed consent form, investigators brochure, and any other relevant supporting information to the appropriate IEC or IRB for review and approval before study initiation. Amendments to the protocol were approved by the IEC/IRB and the local regulatory agencies, as appropriate, before the implementation of changes to the study. The investigator or his/her designee informed the subject of all aspects pertaining to the subject's participation in the study before any screening procedures or investigational drug was administered.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 December 2009
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: 7
Country: Number of subjects enrolled	Canada: 6
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	United States: 51
Worldwide total number of subjects	66
EEA total number of subjects	2

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)	37
Adolescents (12-17 years)	28
Adults (18-64 years)	1
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 28 centers in Australia, Canada, Spain, and the United States. Participants were enrolled from 30 December 2009 until 19 February 2015.

Pre-assignment

Screening details:

Pediatric subjects who completed a romiplostim study for the treatment of thrombocytopenia in pediatric subjects with ITP were eligible to participate in this study.

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
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Arm description:

Participants received romiplostim administered by subcutaneous injection once a week. The starting dose of romiplostim was 1 µg/kg; weekly dose increases continued in increments of 1 µg/kg/week to a maximum dose of 10 µg/kg in an attempt to reach a target platelet count of between $50 \times 10^9/L$ and $200 \times 10^9/L$.

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 with a starting dose of 1 µg/kg/week up to a maximum dose of 10 µg/kg.

Number of subjects in period 1	Romiplostim
Started	66
Received Treatment	65
Completed	39
Not completed	27
Consent withdrawn by subject	11
Administrative decision	5
Adverse event	1
Protocol Specified Criteria	1
Noncompliance	4
Requirement for alternative therapy	5

Baseline characteristics

Reporting groups

Reporting group title	Overall Study
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Reporting group description: -

Reporting group values	Overall Study	Total	
Number of subjects	66	66	
Age Categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	37	37	
Adolescents (12-17 years)	28	28	
Adults (18-64 years)	1	1	
From 65-84 years	0	0	
85 years and over	0	0	
Age Continuous			
Units: years			
arithmetic mean	10.3		
standard deviation	± 4.2	-	
Gender Categorical			
Units: Subjects			
Female	37	37	
Male	29	29	
Race			
Units: Subjects			
White or Caucasian	40	40	
Black or African American	9	9	
Hispanic or Latino	9	9	
Asian	6	6	
Japanese	0	0	
American Indian or Alaska Native	0	0	
Native Hawaiian or Other Pacific Islander	0	0	
Aborigine	0	0	
Other	2	2	

End points

End points reporting groups

Reporting group title	Romiplostim
Reporting group description: Participants received romiplostim administered by subcutaneous injection once a week. The starting dose of romiplostim was 1 µg/kg; weekly dose increases continued in increments of 1 µg/kg/week to a maximum dose of 10 µg/kg in an attempt to reach a target platelet count of between 50 x 10 ⁹ /L and 200 x 10 ⁹ /L.	

Primary: Number of Participants with Adverse Events

End point title	Number of Participants with Adverse Events ^[1]
End point description: The adverse event severity grading scale used was the Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 grading scale. A serious adverse event was defined as an adverse event that met at least one of the following serious criteria: • fatal • life threatening (places the subject at immediate risk of death) • 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. The investigator assessed whether each adverse event was possibly related to the investigational product.	
End point type	Primary
End point timeframe: From first dose of study drug until 1 week after last dose. The median (Q1, Q3) duration of treatment was 135.0 weeks (95.0 weeks, 184.0 weeks).	

Notes:

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

Justification: No hypotheses were tested. The statistical analysis in this open-label extension study were descriptive in nature.

End point values	Romiplostim			
Subject group type	Reporting group			
Number of subjects analysed	65 ^[2]			
Units: participants				
All adverse events (AEs)	64			
Serious adverse events	19			
AEs leading to discontinuation of study drug	2			
AEs leading to withdrawal from study	1			
Grade 3 adverse events	21			
Grade 4 adverse events	5			
Grade 5 adverse events	0			
Treatment-related adverse events (TRAEs)	17			
Treatment-related serious adverse events	1			
TRAEs leading to discontinuation of study drug	0			
TRAEs leading to withdrawal from study	0			

Grade 3 treatment-related adverse events	3			
Grade 4 treatment-related adverse events	1			
Grade 5 treatment-related adverse events	0			

Notes:

[2] - Enrolled participants who received at least one dose of romiplostim.

Statistical analyses

No statistical analyses for this end point

Primary: Duration Adjusted Rate of Treatment Emergent Adverse Events

End point title	Duration Adjusted Rate of Treatment Emergent Adverse
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End point description:

Exposure adjusted rate was defined as total number of events divided by duration of time when subjects were under observation.

End point type	Primary
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End point timeframe:

From first dose of study drug up to 1 week after the last dose. The median (Q1, Q3) duration of treatment was 135.0 weeks (95.0 weeks, 184.0 weeks).

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: No hypotheses were tested. The statistical analysis in this open-label extension study were descriptive in nature.

End point values	Romiplostim			
Subject group type	Reporting group			
Number of subjects analysed	65 ^[4]			
Units: events per 100 subject-years				
number (not applicable)				
All adverse events (AEs)	1397.2			
Serious adverse events	29.7			
AEs leading to discontinuation of study drug	2.8			
AEs leading to withdrawal from study	0.6			
Grade 3 adverse events	38.5			
Grade 4 adverse events	6.6			
Grade 5 adverse events	0			
Treatment-related adverse events (TRAEs)	24.2			
Serious treatment-related adverse events	1.7			
TRAEs leading to discontinuation of study drug	0			
TRAEs leading to withdrawal from study	0			
Grade 3 treatment-related adverse events	2.8			
Grade 4 treatment-related adverse events	0.6			
Grade 5 treatment-related adverse events	0			

Notes:

[4] - Total subject years on study = 181.8

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants who Developed Antibodies to Romiplostim

End point title	Number of Participants who Developed Antibodies to Romiplostim ^[5]
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End point description:

Two validated assays were used to test for antibodies to romiplostim / the thrombopoietin-mimetic peptide component of romiplostim (TMP). The first was an immunoassay to confirm the presence of antibodies. The second was a cell-based bioassay to detect neutralizing or inhibitory effects in vitro. If a sample was positive in both assays, a participant was defined as positive for neutralizing antibodies. Transient antibodies are those positive post-baseline but negative at the last time point tested. Persistent antibodies were those positive at the last time point tested.

End point type	Primary
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End point timeframe:

Once a year until the end of treatment

Notes:

[5] - 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: No hypotheses were tested. The statistical analysis in this open-label extension study were descriptive in nature.

End point values	Romiplostim			
Subject group type	Reporting group			
Number of subjects analysed	64 ^[6]			
Units: participants				
Binding antibodies to romiplostim	5			
Transient binding antibodies to romiplostim	4			
Persistent binding antibodies to romiplostim	1			
Neutralizing antibodies to romiplostim	1			
Transient neutralizing antibodies to romiplostim	0			
Persistent neutralizing antibodies to romiplostim	1			

Notes:

[6] - Subjects with a post-baseline result

Statistical analyses

No statistical analyses for this end point

Primary: Number of Participants who Developed Antibodies to Endogenous Thrombopoietin

End point title	Number of Participants who Developed Antibodies to Endogenous Thrombopoietin ^[7]
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End point description:

Two validated assays were used to test for antibodies to endogenous thrombopoietin (TPO). The first was an immunoassay to confirm the presence of antibodies. The second was a cell-based bioassay to detect neutralizing or inhibitory effects in vitro. If a sample was positive in both assays, a participant was defined as positive for neutralizing antibodies.

Transient antibodies are those positive post-baseline but negative at the last time point tested.

Persistent antibodies were those positive at the last time point tested.

End point type	Primary
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End point timeframe:

Once a year until the end of treatment

Notes:

[7] - 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: No hypotheses were tested. The statistical analysis in this open-label extension study were descriptive in nature.

End point values	Romiplostim			
Subject group type	Reporting group			
Number of subjects analysed	64 ^[8]			
Units: participants				
Binding antibodies to TPO	2			
Transient binding antibodies to TPO	2			
Persistent binding antibodies to TPO	0			
Neutralizing antibodies to TPO	0			
Transient neutralizing antibodies to TPO	0			
Persistent neutralizing antibodies to TPO	0			

Notes:

[8] - Subjects with a post-baseline result

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants with a Platelet Response

End point title	Percentage of Participants with a Platelet Response
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End point description:

Platelet response was defined as any platelet counts $\geq 50 \times 10^9/L$ in the absence of rescue medication

End point type	Secondary
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End point timeframe:

Every 4 weeks for the duration of treatment

End point values	Romiplostim			
Subject group type	Reporting group			
Number of subjects analysed	65 ^[9]			
Units: percentage of participants				
number (confidence interval 95%)	93.8 (85 to 98.3)			

Notes:

[9] - Enrolled participants who received at least one dose of romiplostim.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Participants who used Concomitant ITP Therapy

End point title	Percentage of Participants who used Concomitant ITP Therapy
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End point description:

End point type	Secondary
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End point timeframe:

From baseline to the end of treatment

End point values	Romiplostim			
Subject group type	Reporting group			
Number of subjects analysed	65 ^[10]			
Units: percentage of participants				
number (confidence interval 95%)	47.7 (35.1 to 60.5)			

Notes:

[10] - Enrolled participants who received at least one dose of romiplostim.

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 until 1 week after last dose. The median (Q1, Q3) duration of treatment was 135.0 weeks (95.0 weeks, 184.0 weeks).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.1
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Reporting groups

Reporting group title	Romiplostim
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Reporting group description:

Participants received romiplostim administered by subcutaneous injection once a week. The starting dose of romiplostim was 1 µg/kg; weekly dose increases continued in increments of 1 µg/kg/week to a maximum dose of 10 µg/kg in an attempt to reach a target platelet count of between 50 x 10⁹/L and 200 x 10⁹/L.

Serious adverse events	Romiplostim		
Total subjects affected by serious adverse events			
subjects affected / exposed	19 / 65 (29.23%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Haemangioma			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pyrexia			

subjects affected / exposed	3 / 65 (4.62%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Ulcer haemorrhage			
subjects affected / exposed	1 / 65 (1.54%)		
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	2 / 65 (3.08%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Asthma			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicidal ideation			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Platelet count decreased			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 6		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Contusion			

subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Head injury			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Post procedural haemorrhage			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Transfusion reaction			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 65 (3.08%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Febrile neutropenia			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Leukopenia			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune thrombocytopenic purpura			

subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			
subjects affected / exposed	4 / 65 (6.15%)		
occurrences causally related to treatment / all	1 / 6		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Mouth haemorrhage			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Vomiting			
subjects affected / exposed	2 / 65 (3.08%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Biliary dyskinesia			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Gastroenteritis			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal infection			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Clostridium difficile infection			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Infection				
subjects affected / exposed	1 / 65 (1.54%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Gingivitis				
subjects affected / exposed	1 / 65 (1.54%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Meningitis viral				
subjects affected / exposed	1 / 65 (1.54%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Metapneumovirus infection				
subjects affected / exposed	1 / 65 (1.54%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Pneumonia mycoplasmal				
subjects affected / exposed	1 / 65 (1.54%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pharyngitis streptococcal				
subjects affected / exposed	1 / 65 (1.54%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Viral infection				
subjects affected / exposed	1 / 65 (1.54%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Subcutaneous abscess				
subjects affected / exposed	1 / 65 (1.54%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory syncytial virus infection				

subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 65 (1.54%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	1 / 65 (1.54%)		
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	64 / 65 (98.46%)		
Vascular disorders			
Haematoma			
subjects affected / exposed	4 / 65 (6.15%)		
occurrences (all)	13		
Haemorrhage			
subjects affected / exposed	4 / 65 (6.15%)		
occurrences (all)	5		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	4 / 65 (6.15%)		
occurrences (all)	4		
Fatigue			
subjects affected / exposed	15 / 65 (23.08%)		
occurrences (all)	32		
Injection site bruising			
subjects affected / exposed	6 / 65 (9.23%)		
occurrences (all)	9		

Pain subjects affected / exposed occurrences (all)	8 / 65 (12.31%) 10		
Pyrexia subjects affected / exposed occurrences (all)	28 / 65 (43.08%) 76		
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	8 / 65 (12.31%) 8		
Reproductive system and breast disorders Dysmenorrhoea subjects affected / exposed occurrences (all)	7 / 65 (10.77%) 15		
Respiratory, thoracic and mediastinal disorders Asthma subjects affected / exposed occurrences (all)	4 / 65 (6.15%) 4		
Cough subjects affected / exposed occurrences (all)	30 / 65 (46.15%) 63		
Epistaxis subjects affected / exposed occurrences (all)	31 / 65 (47.69%) 101		
Nasal congestion subjects affected / exposed occurrences (all)	22 / 65 (33.85%) 33		
Oropharyngeal pain subjects affected / exposed occurrences (all)	30 / 65 (46.15%) 80		
Rhinitis allergic subjects affected / exposed occurrences (all)	4 / 65 (6.15%) 4		
Rhinorrhoea subjects affected / exposed occurrences (all)	19 / 65 (29.23%) 29		

Psychiatric disorders			
Anxiety			
subjects affected / exposed	4 / 65 (6.15%)		
occurrences (all)	6		
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	32 / 65 (49.23%)		
occurrences (all)	434		
Arthropod bite			
subjects affected / exposed	7 / 65 (10.77%)		
occurrences (all)	8		
Fall			
subjects affected / exposed	5 / 65 (7.69%)		
occurrences (all)	13		
Head injury			
subjects affected / exposed	5 / 65 (7.69%)		
occurrences (all)	6		
Laceration			
subjects affected / exposed	10 / 65 (15.38%)		
occurrences (all)	11		
Ligament sprain			
subjects affected / exposed	7 / 65 (10.77%)		
occurrences (all)	13		
Limb injury			
subjects affected / exposed	4 / 65 (6.15%)		
occurrences (all)	4		
Procedural pain			
subjects affected / exposed	6 / 65 (9.23%)		
occurrences (all)	8		
Scratch			
subjects affected / exposed	7 / 65 (10.77%)		
occurrences (all)	10		
Skin abrasion			
subjects affected / exposed	15 / 65 (23.08%)		
occurrences (all)	29		
Cardiac disorders			

Tachycardia subjects affected / exposed occurrences (all)	4 / 65 (6.15%) 4		
Nervous system disorders Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all) Paraesthesia subjects affected / exposed occurrences (all)	11 / 65 (16.92%) 14 38 / 65 (58.46%) 149 4 / 65 (6.15%) 8		
Blood and lymphatic system disorders Thrombocytopenia subjects affected / exposed occurrences (all) Lymphadenopathy subjects affected / exposed occurrences (all)	4 / 65 (6.15%) 4 4 / 65 (6.15%) 5		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all)	9 / 65 (13.85%) 14		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	12 / 65 (18.46%) 19 11 / 65 (16.92%) 19 20 / 65 (30.77%) 32 20 / 65 (30.77%) 32		

Gingival bleeding subjects affected / exposed occurrences (all)	13 / 65 (20.00%) 21		
Gingival pain subjects affected / exposed occurrences (all)	4 / 65 (6.15%) 8		
Mouth haemorrhage subjects affected / exposed occurrences (all)	9 / 65 (13.85%) 22		
Nausea subjects affected / exposed occurrences (all)	24 / 65 (36.92%) 36		
Vomiting subjects affected / exposed occurrences (all)	32 / 65 (49.23%) 60		
Skin and subcutaneous tissue disorders			
Acne subjects affected / exposed occurrences (all)	4 / 65 (6.15%) 5		
Petechiae subjects affected / exposed occurrences (all)	20 / 65 (30.77%) 117		
Ecchymosis subjects affected / exposed occurrences (all)	8 / 65 (12.31%) 13		
Purpura subjects affected / exposed occurrences (all)	4 / 65 (6.15%) 7		
Rash subjects affected / exposed occurrences (all)	14 / 65 (21.54%) 24		
Skin lesion subjects affected / exposed occurrences (all)	5 / 65 (7.69%) 5		
Musculoskeletal and connective tissue disorders			

Arthralgia			
subjects affected / exposed	15 / 65 (23.08%)		
occurrences (all)	27		
Back pain			
subjects affected / exposed	11 / 65 (16.92%)		
occurrences (all)	15		
Joint swelling			
subjects affected / exposed	4 / 65 (6.15%)		
occurrences (all)	4		
Musculoskeletal pain			
subjects affected / exposed	4 / 65 (6.15%)		
occurrences (all)	4		
Myalgia			
subjects affected / exposed	6 / 65 (9.23%)		
occurrences (all)	6		
Neck pain			
subjects affected / exposed	7 / 65 (10.77%)		
occurrences (all)	7		
Pain in extremity			
subjects affected / exposed	14 / 65 (21.54%)		
occurrences (all)	22		
Infections and infestations			
Bronchitis			
subjects affected / exposed	5 / 65 (7.69%)		
occurrences (all)	5		
Conjunctivitis			
subjects affected / exposed	7 / 65 (10.77%)		
occurrences (all)	7		
Ear infection			
subjects affected / exposed	7 / 65 (10.77%)		
occurrences (all)	8		
Gastroenteritis viral			
subjects affected / exposed	6 / 65 (9.23%)		
occurrences (all)	6		
Influenza			

subjects affected / exposed	10 / 65 (15.38%)		
occurrences (all)	11		
Nasopharyngitis			
subjects affected / exposed	22 / 65 (33.85%)		
occurrences (all)	67		
Pharyngitis streptococcal			
subjects affected / exposed	13 / 65 (20.00%)		
occurrences (all)	19		
Sinusitis			
subjects affected / exposed	5 / 65 (7.69%)		
occurrences (all)	5		
Tonsillitis			
subjects affected / exposed	4 / 65 (6.15%)		
occurrences (all)	5		
Upper respiratory tract infection			
subjects affected / exposed	32 / 65 (49.23%)		
occurrences (all)	101		
Urinary tract infection			
subjects affected / exposed	4 / 65 (6.15%)		
occurrences (all)	6		
Viral infection			
subjects affected / exposed	5 / 65 (7.69%)		
occurrences (all)	8		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	6 / 65 (9.23%)		
occurrences (all)	17		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 December 2011	• The sample size was increased from 20 subjects to approximately 100 subjects. • The sample size was increased from 20 subjects to approximately 100 subjects. • 36 months treatment duration was added. • Inclusion/exclusion criteria were updated. • An end of follow-up visit was added. • Information about consenting to participate in an optional PK portion of the study was added. • The number of study centers was increased from 10 to 50 centers. • The study completion date was changed from December 2012 to December 2014. • The dosage (and adjustments), administration, and schedule were clarified. • Medications were added to the list of permitted rescue medications. • Medications were added to the list of prohibited medications. • The laboratory sample collection and shipping instructions were changed to include the additional collections of blood smears, biopsies, or aspirate, if necessary. • The collection of antibody samples was added. • The activities occurring at the study were clarified. • Reporting procedures for adverse events were clarified.
20 March 2012	• The pharmacy guide in Appendix E was removed and replaced with the Investigational Product Information Manual to accommodate study center-specific drug distribution options and to ensure that the most current investigational product details were accurately communicated. • The serious adverse event guidance was updated to reflect a 24-hour rather than 1 work day timeline for reporting serious adverse events.
25 September 2012	• Study contacts and other minor updates were made. • The definition of the study duration for subjects was updated. • The serious adverse event reporting language was updated per current Amgen safety guidelines. • The adverse event reporting language and grading criteria (National Cancer Institute - Common Terminology Criteria for Adverse Events [CTCAE] version 3.0) were changed for consistency within the romiplostim pediatric program.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported