Clinical trial results:
A Phase 2, Interventional, Single Arm Study Describing Platelet Responses and ITP Remission Rates in Adult Subjects with Immune Thrombocytopenia Purpura Receiving Romiplostim

Summary

EudraCT number	2010-019987-35
Trial protocol	IT DE GB ES FR CZ
Global end of trial date	26 December 2013

Results information

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	30 July 2015

Trial information

Trial identification

Sponsor protocol code	20080435

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01143038
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, United States, 91320
Public contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com
Scientific contact	IHQ Medical Info-Clinical Trials, Amgen (EUROPE) GmbH, MedInfoInternational@amgen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	26 December 2013
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	26 December 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To describe the number of months with a subject platelet response over a 12 month treatment period

Protection of trial subjects:

This study was conducted in accordance with applicable FDA and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines. A copy of the protocol, the proposed informed consent, and all other subject information and/or recruitment materials were submitted to the IEC or IRB of each study center for approval. The investigator or a designee obtained 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	30 November 2010
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	Poland: 15
Country: Number of subjects enrolled	Spain: 8
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Czech Republic: 12
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 11
Country: Number of subjects enrolled	Italy: 11
Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	United States: 7
Worldwide total number of subjects	75
EEA total number of subjects	65

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	61
From 65 to 84 years	12
85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Ninety-eight adult subjects with ITP were screened for the study; 23 subjects were considered screen failures. Seventy-five subjects were enrolled and received at least 1 dose of romiplostim.

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 during the 12-month treatment period. The starting dose was 1 µg/kg with 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 ≥ 50 x 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:

Romiplostim was administered weekly by subcutaneous injection. 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 ≥ 50 x 10^9/L. Dose adjustments were allowed during the treatment period to maintain a platelet count between 50 x 10^9/L and 200 x 10^9/L.

Number of subjects in period 1	Romiplostim
Started	75
Completed	59
Not completed	16
Consent withdrawn by subject	4
Death	1
Other	1
Adverse event	3
Lost to follow-up	2
Requirement for alternative therapy	4
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Romiplostim
Reporting group description:	
Participants received romiplostim administered weekly by subcutaneous injection during the 12-month treatment period. The starting dose was 1 µg/kg with 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 ≥ 50 x 10^9/L.	

Reporting group values	Romiplostim	Total	
Number of subjects	75	75	
Age categorical Units: Subjects			
< 65 years	61	61	
≥ 65 years	14	14	
Age continuous Units: years			
arithmetic mean	44.5		
standard deviation	± 18.17	-	
Gender categorical Units: Subjects			
Female	44	44	
Male	31	31	
Race Units: Subjects			
American Indian or Alaska Native	0	0	
Asian	1	1	
Black (or African American)	1	1	
Native Hawaiian or Other Pacific Islander	0	0	
White	72	72	
Other	0	0	
Unknown	1	1	
Ethnicity Units: Subjects			
Hispanic/Latino	6	6	
Not Hispanic/Latino	69	69	
Time since ITP diagnosis Units: months			
median	2.2		
full range (min-max)	0.1 to 6.6	-	
Platelet count at screening Units: x10^9/L			
arithmetic mean	19.78		
standard deviation	± 15.8	-	

End points

End points reporting groups

Reporting group title	Romiplostim

Reporting group description:

Participants received romiplostim administered weekly by subcutaneous injection during the 12-month treatment period. The starting dose was 1 µg/kg with 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 ≥ 50 x 10^9/L.

Primary: Number of Months with Platelet Response During the 12-Month Treatment period

End point title	Number of Months with Platelet Response During the 12-Month Treatment period[1]

End point description:

The primary endpoint was the number of months a subject achieved a platelet response during the 12-month treatment period. A platelet response for any 1 month was defined as the median of platelet counts measured in the month ≥ 50 x 10^9/L.
Platelet counts within 4 weeks following a rescue medication use or following splenectomy were considered non-response. Months without any platelet count measurement and months following splenectomy were considered as months with no platelet response.
Safety Analysis Set includes all subjects who have received at least 1 dose of romiplostim.

End point type	Primary

End point timeframe:

12 months

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: A formal hypothesis was not tested in this study. The primary analysis of the primary and secondary endpoints was descriptive.

End point values	Romiplostim			
Subject group type	Reporting group			
Number of subjects analysed	75[2]			
Units: months				
arithmetic mean (standard error)	9.2 (± 0.4)			

Notes:

[2] - Safety Analysis Set

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with ITP remisssion

End point title	Percentage of subjects with ITP remisssion

End point description:

ITP remission was defined as all platelet counts ≥ 50 x 10^9/L in the absence of romiplostim and all other therapies dosed with the intent to treat ITP for at least 6 months.

End point type	Secondary

End point timeframe:

12 months

End point values	Romiplostim			
Subject group type	Reporting group			
Number of subjects analysed	75[3]			
Units: percentage of subjects				
number (confidence interval 95%)	32 (21.7 to 43.8)			

Notes:

[3] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of subjects with splenectomy during the 12-month treatment period

End point title	Percentage of subjects with splenectomy during the 12-month treatment period

End point description:

End point type	Secondary

End point timeframe:

12 months

End point values	Romiplostim			
Subject group type	Reporting group			
Number of subjects analysed	75[4]			
Units: percentage of subjects				
number (confidence interval 95%)	1.3 (0 to 7.2)			

Notes:

[4] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects who developed antibodies to romiplostim

End point title	Number of subjects who developed antibodies to romiplostim

End point description:

The number of subjects developing antibody formation (defined as negative at baseline and positive at post-baseline, transient or persistent) to romiplostim, endogenous thrombopoietin (eTPO), and thrombopoietin mimetic peptide (TMP, the peptide component of romiplostim) was summarized

End point type	Secondary

End point timeframe:

12 months

End point values	Romiplostim			
Subject group type	Reporting group			
Number of subjects analysed	69[5]			
Units: subjects				
Antibodies to romiplostim	2			
Antibodies to TPO	1			
Antibodies to TMP	2			
Neutralizing antibodies to romiplostim	1			
Neutralizing antibodies to TPO	0			
Neutralizing antibodies to TMP	0			

Notes:

[5] - Safety analysis set participants with available results

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects with adverse events

End point title	Number of subjects with adverse events

End point description:

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. A serious adverse event is defined as an adverse event that meets at least one of the following serious criteria:
• fatal
• life threatening (places the subject at immediate risk of death)
• requires in-patient hospitalization or prolongation of existing hospitalization
• results in persistent or significant disability/incapacity
• congenital anomaly/birth defect
• other significant medical hazard.
Whether an adverse event was treatment related (TRAE) or not was determined by investigator.

End point type	Secondary

End point timeframe:

From first dose date of romiplostim to end of study (up to 24 months).

End point values	Romiplostim			
Subject group type	Reporting group			
Number of subjects analysed	75[6]			
Units: subjects				
All treatment-emergent adverse events	63			
Serious adverse events	17			
Leading to discontinuation of romiplostim	4			
Leading to discontinuation from study	3			
Fatal adverse events	0			
Treatment-related treatment-emergent adverse event	21			

Treatment-related serious adverse events	3			
TRAEs leading to discontinuation of romiplostim	2			
TRAEs leading to discontinuation from study	2			
Treatment-related fatal adverse events	0			

Notes:

[6] - Safety analysis set

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From first dose date of romiplostim to end of study (up to 24 months)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups	
Reporting group title	Romiplostim

Reporting group description:

Participants received romiplostim administered weekly by subcutaneous injection during the 12-month treatment period. The starting dose was 1 µg/kg with 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 ≥ 50 x 10^9/L.

Serious adverse events	Romiplostim		
Total subjects affected by serious adverse events			
subjects affected / exposed	17 / 75 (22.67%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Non-Hodgkin's lymphoma			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Papillary thyroid cancer			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Peripheral vascular disorder			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pleuritic pain			

subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Delirium tremens			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Transaminases increased			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Tendon rupture			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Reversible ischaemic neurological deficit			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Idiopathic thrombocytopenic purpura			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			

subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Faecaloma			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastritis			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Dapsone syndrome			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Renal failure acute			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	1 / 75 (1.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Erysipelas			

subjects affected / exposed	1 / 75 (1.33%)		
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	50 / 75 (66.67%)		
Vascular disorders			
Haematoma			
subjects affected / exposed	8 / 75 (10.67%)		
occurrences (all)	9		
Hypertension			
subjects affected / exposed	6 / 75 (8.00%)		
occurrences (all)	7		
Nervous system disorders			
Dizziness			
subjects affected / exposed	4 / 75 (5.33%)		
occurrences (all)	5		
Headache			
subjects affected / exposed	13 / 75 (17.33%)		
occurrences (all)	18		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	5 / 75 (6.67%)		
occurrences (all)	6		
Fatigue			
subjects affected / exposed	6 / 75 (8.00%)		
occurrences (all)	7		
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	4 / 75 (5.33%)		
occurrences (all)	7		
Eye disorders			

Conjunctivitis			
subjects affected / exposed	4 / 75 (5.33%)		
occurrences (all)	4		
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	4 / 75 (5.33%)		
occurrences (all)	4		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	7 / 75 (9.33%)		
occurrences (all)	7		
Epistaxis			
subjects affected / exposed	6 / 75 (8.00%)		
occurrences (all)	8		
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	4 / 75 (5.33%)		
occurrences (all)	5		
Petechiae			
subjects affected / exposed	7 / 75 (9.33%)		
occurrences (all)	13		
Rash			
subjects affected / exposed	4 / 75 (5.33%)		
occurrences (all)	6		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	11 / 75 (14.67%)		
occurrences (all)	14		
Myalgia			
subjects affected / exposed	4 / 75 (5.33%)		
occurrences (all)	4		
Infections and infestations			
Influenza			
subjects affected / exposed	7 / 75 (9.33%)		
occurrences (all)	10		
Nasopharyngitis			

subjects affected / exposed	10 / 75 (13.33%)		
occurrences (all)	11		
Rhinitis			
subjects affected / exposed	4 / 75 (5.33%)		
occurrences (all)	5		
Upper respiratory tract infection			
subjects affected / exposed	6 / 75 (8.00%)		
occurrences (all)	9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 January 2013	- The study schema was updated to illustrate and clarify the various treatment scenarios. - Clarification was made to describe the various treatment periods and their definitions. - Clarification was made in the language throughout the protocol for medications for ITP given either concomitantly or as rescue medications. - Updates to pregnancy, antibody testing parameters, and contraception requirements were updated per the current Amgen requirements. - Updates were made to the serious adverse event reporting language in Section 9.2 per the current Amgen safety requirements.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported