Clinical trial results:
A Randomized, Double-Blind, Placebo-controlled Phase 1/2 Study to Determine the Safety and Efficacy of Romiplostim (AMG 531) in Thrombocytopenic Pediatric Subjects with Chronic Immune (Idiopathic) Thrombocytopenic Purpura

Summary

EudraCT number	2007-003569-42
Trial protocol	ES
Global end of trial date	03 March 2009

Results information

Result version number	v1 (current)
This version publication date	20 June 2016
First version publication date	06 August 2015

Trial information

Trial identification

Sponsor protocol code	20060195

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00515203
WHO universal trial number (UTN)	-

Notes:

Sponsors

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

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	
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	03 March 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 March 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The purpose of this study is to evaluate the safety and tolerability of romiplostim (AMG 531) in the treatment of thrombocytopenia in pediatric subjects with chronic ITP. We will also evaluate the efficacy of romiplostim (AMG 531) and characterize the pharmacokinetics of romiplostim (AMG 531). It is anticipated that romiplostim (AMG 531), when given at an effective dose and schedule, will be well tolerated treatment for thrombocytopenia among pediatric subjects with chronic ITP.

Protection of trial subjects:

This study was conducted in accordance with appropriate country regulations and the International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidelines. Essential documents will be retained in accordance with ICH GCP.
Before any subject participated in the study, the investigator was to obtain written informed consent from the subject or legally acceptable representative following adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. Informed consent was to be obtained before any protocol-specific screening procedures or administration of investigational product. In addition to written informed consent, the assent of the child from those subjects capable of providing assent must have been obtained if requested by the IRB/IEC.
Copies of the protocol, informed consent form, and other written subject information were submitted to the IEC or IRB for written approval. A copy of the written approval of the protocol and informed consent form was received by Amgen before recruitment of subjects into the study and shipment of investigational product.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 July 2007
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	Spain: 2
Country: Number of subjects enrolled	United States: 18
Country: Number of subjects enrolled	Australia: 2
Worldwide total number of subjects	22
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)	2
Children (2-11 years)	12
Adolescents (12-17 years)	8
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled from 19 Jul 2007 through 11 November 2008

Pre-assignment

Screening details:

Subjects were boys and girls aged 12 months to < 18 years with ITP diagnosed at least 6 months prior to screening and severe thrombocytopenia (mean of 2 screening platelet counts ≤ 30 x 10^9/L with no single count > 35 x 10^9/L). Concurrent corticosteroid therapy was allowed.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Placebo by subcutaneous injection once weekly

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Administered by subcutaneous injection

Arm title	Romiplostim

Arm description:

Romiplostim by subcutaneous injection once weekly at a starting dose of 1 µg/kg, adjusted based on weekly platelet counts to a maximum weekly dose of 10 µg/kg.

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

Number of subjects in period 1	Placebo	Romiplostim
Started	5	17
Completed	5	17

Baseline characteristics

Reporting groups	
Reporting group title	Romiplostim
Reporting group description:	
Romiplostim by subcutaneous injection once weekly at a starting dose of 1 µg/kg, adjusted based on weekly platelet counts to a maximum weekly dose of 10 µg/kg.	
Reporting group title	Placebo
Reporting group description:	
Placebo by subcutaneous injection once weekly	

Reporting group values	Romiplostim	Placebo	Total
Number of subjects	17	5	22
Age categorical Units: Subjects			
12 months to < 3 years	3	1	4
3 years to < 12 years	8	2	10
12 years to < 18 years	6	2	8
Age Continuous Units: Years			
arithmetic mean	9.4	9.8	
standard deviation	± 5.4	± 4.6	-
Gender, Male/Female Units: Participants			
Female	4	2	6
Male	13	3	16
Race, Customized Units: Subjects			
White or Caucasian	9	4	13
Black or African American	5	0	5
Hispanic or Latino	3	0	3
Other	0	1	1

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo by subcutaneous injection once weekly	
Reporting group title	Romiplostim
Reporting group description:	
Romiplostim by subcutaneous injection once weekly at a starting dose of 1 µg/kg, adjusted based on weekly platelet counts to a maximum weekly dose of 10 µg/kg.	

Primary: Adverse Events

End point title	Adverse Events[1]
End point description:	
Occurrence of one or more adverse events in the participant during the 12-week treatment period.	
End point type	Primary
End point timeframe:	
12 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: The nature of analyses for this endpoint was descriptive and no formal hypothesis testing was performed.

End point values	Romiplostim	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	5		
Units: Participants				
number (not applicable)	16	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Weeks with Platelet Count ≥ 50 x 10^9/L

End point title	Weeks with Platelet Count ≥ 50 x 10^9/L
End point description:	
The number of weeks with platelet count ≥ 50 x 10^9/L during the 12 week treatment period.	
End point type	Secondary
End point timeframe:	
12-week treatment period	

End point values	Romiplostim	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	5		
Units: Weeks				
arithmetic mean (standard deviation)	5.65 (± 3)	0 (± 0)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Romiplostim v Placebo
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0019
Method	Cochran-Mantel-Haenszel

Secondary: Bleeding Events (Grade 2 or higher)

End point title	Bleeding Events (Grade 2 or higher)

End point description:

Total number of bleeding events (Grade 2 or higher, i.e., mild to life-threatening, as defined in the protocol) for each participant during Weeks 2-13 (end-of-study visit for non-responders)

End point type	Secondary

End point timeframe:

12-week treatment period (Weeks 2 - 13)

End point values	Romiplostim	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	5		
Units: Events per participant				
arithmetic mean (standard deviation)	0.41 (± 1)	0 (± 0)		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Romiplostim v Placebo

Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3651
Method	Cochran-Mantel-Haenszel

Secondary: Platelet count ≥ 50 x 10^9/L for two consecutive weeks

End point title	Platelet count ≥ 50 x 10^9/L for two consecutive weeks

End point description:

Participant incidence of achieving a platelet count ≥50 x 10^9/L for two consecutive weeks during the 12 week treatment period.

End point type	Secondary

End point timeframe:

12-week treatment period

End point values	Romiplostim	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	5		
Units: Participants				
number (not applicable)	15	0		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Romiplostim v Placebo
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0008
Method	Fisher exact

Secondary: Increase in platelet count ≥ 20 x 10^9/L above baseline for two consecutive weeks

End point title	Increase in platelet count ≥ 20 x 10^9/L above baseline for two consecutive weeks

End point description:

Participant incidence of achieving an increase in platelet count ≥20 x 10^9/L above baseline for two consecutive weeks during the 12 week treatment period.

End point type	Secondary

End point timeframe:

12-week treatment period

End point values	Romiplostim	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	5		
Units: Participants				
number (not applicable)	15	0		

Statistical analyses

Statistical analysis title	Statisticla Analysis
Comparison groups	Romiplostim v Placebo
Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0008
Method	Fisher exact

Secondary: Requirement for Rescue Therapy (as defined per protocol)	
End point title	Requirement for Rescue Therapy (as defined per protocol)
End point description: Participant required rescue therapy (as defined per protocol) during the 12 week treatment period.	
End point type	Secondary
End point timeframe: 12-week treatment period	

End point values	Romiplostim	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	17	5		
Units: Participants				
number (not applicable)	2	2		

Statistical analyses

Statistical analysis title	Statistical Analysis
Comparison groups	Romiplostim v Placebo

Number of subjects included in analysis	22
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2098
Method	Fisher exact

Adverse events

Adverse events information

Timeframe for reporting adverse events:

16 weeks

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo by subcutaneous injection once weekly

Reporting group title	Romiplostim

Reporting group description:

Romiplostim by subcutaneous injection once weekly at a starting dose of 1 µg/kg, adjusted based on weekly platelet counts to a maximum weekly dose of 10 µg/kg

Serious adverse events	Placebo	Romiplostim	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 5 (0.00%)	2 / 17 (11.76%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Blood and lymphatic system disorders			
Lymphadenitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Influenza			
subjects affected / exposed	0 / 5 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Sepsis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 17 (5.88%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Romiplostim	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 5 (100.00%)	16 / 17 (94.12%)	
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 5 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	0 / 5 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Injection site haematoma			
subjects affected / exposed	1 / 5 (20.00%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Injection site haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Malaise			
subjects affected / exposed	1 / 5 (20.00%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	0 / 5 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	0 / 5 (0.00%)	5 / 17 (29.41%)	
occurrences (all)	0	6	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 5 (20.00%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			

Genital haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Menorrhagia			
subjects affected / exposed	0 / 5 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Vaginal discharge			
subjects affected / exposed	0 / 5 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 5 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	2 / 5 (40.00%)	2 / 17 (11.76%)	
occurrences (all)	3	2	
Dyspnoea exertional			
subjects affected / exposed	0 / 5 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Epistaxis			
subjects affected / exposed	1 / 5 (20.00%)	6 / 17 (35.29%)	
occurrences (all)	1	8	
Nasal congestion			
subjects affected / exposed	2 / 5 (40.00%)	0 / 17 (0.00%)	
occurrences (all)	2	0	
Oropharyngeal pain			
subjects affected / exposed	0 / 5 (0.00%)	4 / 17 (23.53%)	
occurrences (all)	0	4	
Pharyngeal erythema			
subjects affected / exposed	1 / 5 (20.00%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Respiratory tract congestion			
subjects affected / exposed	0 / 5 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Rhinorrhoea			

subjects affected / exposed	1 / 5 (20.00%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Wheezing			
subjects affected / exposed	0 / 5 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Psychiatric disorders			
Emotional disorder			
subjects affected / exposed	0 / 5 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Investigations			
Spleen palpable			
subjects affected / exposed	0 / 5 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	1 / 5 (20.00%)	3 / 17 (17.65%)	
occurrences (all)	3	4	
Fall			
subjects affected / exposed	0 / 5 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Scratch			
subjects affected / exposed	1 / 5 (20.00%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Skin laceration			
subjects affected / exposed	1 / 5 (20.00%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 5 (20.00%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Headache			
subjects affected / exposed	2 / 5 (40.00%)	6 / 17 (35.29%)	
occurrences (all)	2	11	
Blood and lymphatic system disorders			
Thrombocytopenia			

subjects affected / exposed	0 / 5 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 5 (20.00%)	1 / 17 (5.88%)	
occurrences (all)	2	1	
Abdominal pain upper			
subjects affected / exposed	0 / 5 (0.00%)	3 / 17 (17.65%)	
occurrences (all)	0	4	
Chapped lips			
subjects affected / exposed	0 / 5 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	0 / 5 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	
Mouth haemorrhage			
subjects affected / exposed	0 / 5 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	0 / 5 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	2 / 5 (40.00%)	2 / 17 (11.76%)	
occurrences (all)	2	2	
Skin and subcutaneous tissue disorders			
Erythema			
subjects affected / exposed	0 / 5 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Hyperhidrosis			
subjects affected / exposed	1 / 5 (20.00%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Petechiae			
subjects affected / exposed	1 / 5 (20.00%)	2 / 17 (11.76%)	
occurrences (all)	2	3	
Pruritus			

subjects affected / exposed	0 / 5 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	4	
Rash			
subjects affected / exposed	0 / 5 (0.00%)	3 / 17 (17.65%)	
occurrences (all)	0	5	
Rash macular			
subjects affected / exposed	0 / 5 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	3	
Skin nodule			
subjects affected / exposed	0 / 5 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 5 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Urethral disorder			
subjects affected / exposed	0 / 5 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 5 (20.00%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	1 / 5 (20.00%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Inguinal mass			
subjects affected / exposed	0 / 5 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	1 / 5 (20.00%)	1 / 17 (5.88%)	
occurrences (all)	1	1	
Infections and infestations			
Ear infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Herpes simplex			

subjects affected / exposed	1 / 5 (20.00%)	0 / 17 (0.00%)	
occurrences (all)	1	0	
Infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	0 / 5 (0.00%)	2 / 17 (11.76%)	
occurrences (all)	0	2	
Otitis media			
subjects affected / exposed	0 / 5 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Otitis media acute			
subjects affected / exposed	0 / 5 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	0 / 5 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	1 / 5 (20.00%)	2 / 17 (11.76%)	
occurrences (all)	2	3	
Urinary tract infection			
subjects affected / exposed	0 / 5 (0.00%)	1 / 17 (5.88%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 August 2007	Major Changes: • Replaced the use of the romiplostim diluent with a commercially available diluent.
04 September 2008	Major Changes: • Updated consent form to provide updated patient exposure numbers and percentage of subjects who have reported adverse events.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported