Clinical trial results:
A Phase 3 Randomized, Double Blind, Placebo Controlled Study to Determine the Safety and Efficacy of Romiplostim in Thrombocytopenic Pediatric Subjects with Immune Thrombocytopenia (ITP)

Summary

EudraCT number	2010-018426-39
Trial protocol	Outside EU/EEA
Global end of trial date	19 February 2015

Results information

Result version number	v1 (current)
This version publication date	03 July 2016
First version publication date	03 July 2016

Trial information

Trial identification

Sponsor protocol code	20080279

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01444417
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 Information-Clinical, Amgen (EUROPE) GmbH, MedinfoInternational@amgen.com
Scientific contact	IHQ Medical Information-Clinical, 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	19 February 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective was to evaluate the efficacy of romiplostim in the treatment of thrombocytopenia in pediatric subjects with immune thrombocytopenia (ITP) as measured by durable platelet response.

Protection of trial subjects:

This study was conducted in accordance with the United States Food and Drug Administration (FDA) and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) regulations/guidelines.
All subjects provided written informed consent before undergoing any study-related procedures, including screening procedures.
The study protocol, amendments, and the informed consent form (ICF) were reviewed by the Institutional Review Boards (IRBs) and Independent Ethics Committees (IECs). No subjects were recruited into the study and no investigational product (IP) was shipped until the IRB/IEC gave written approval of the protocol and ICF and Amgen received copies of these approvals.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	24 January 2012
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 7
Country: Number of subjects enrolled	Australia: 6
Country: Number of subjects enrolled	United States: 49
Worldwide total number of subjects	62
EEA total number of subjects	0

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)	39

Adolescents (12-17 years)	23
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 27 centers in the United States, Canada, and Australia.

Pre-assignment

Screening details:

Subjects who met eligibility criteria were enrolled and stratified by the following 3 age categories: ≥ 1 to < 6 years; 6 to < 12 years; and 12 to < 18 years.

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:

Participants received weekly subcutaneous placebo for 24 weeks.

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:

Matching placebo administered once a week by subcutaneous injection

Arm title	Romiplostim

Arm description:

Participants received once weekly subcutaneous romiplostim for 24 weeks at a starting dose of 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.

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 weekly as a subcutaneous injection.

Number of subjects in period 1	Placebo	Romiplostim
Started	20	42
Received Treatment	19	42
Completed	18	41
Not completed	2	1
Consent withdrawn by subject	2	-
Ineligibility determined	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received weekly subcutaneous placebo for 24 weeks.	
Reporting group title	Romiplostim
Reporting group description:	
Participants received once weekly subcutaneous romiplostim for 24 weeks at a starting dose of 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.	

Reporting group values	Placebo	Romiplostim	Total
Number of subjects	20	42	62
Age categorical Units: Subjects			
≥ 1 - < 6 years	4	8	12
≥ 6 - < 12 years	9	18	27
≥ 12 - < 18 years	7	16	23
Age continuous Units: years			
arithmetic mean	9.4	9.7	
standard deviation	± 4.7	± 4.1	-
Gender categorical Units: Subjects			
Female	11	24	35
Male	9	18	27
Race Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	2	3	5
Black or African American	2	6	8
Multiple	0	1	1
Native Hawaiian or Other Pacific Islander	0	1	1
Other	1	5	6
White	15	26	41
Platelets Units: 10^9/L			
arithmetic mean	19.9	17.5	
standard deviation	± 19.3	± 10.7	-

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Participants received weekly subcutaneous placebo for 24 weeks.	
Reporting group title	Romiplostim
Reporting group description:	
Participants received once weekly subcutaneous romiplostim for 24 weeks at a starting dose of 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.	

Primary: Percentage of Participants with a Durable Platelet Response

End point title	Percentage of Participants with a Durable Platelet Response
End point description:	
A participant with durable platelet response was defined as achieving at least 6 weekly platelet counts of ≥ 50 x 10^9/L during the last 8 weeks of treatment (platelet counts obtained from week 18 to week 25). If a platelet count from a participant was not available (missing) in a certain week, that week was imputed as non-response for that participant. Platelet counts were not deemed as a positive response for 4 weeks after the administration of rescue medication.	
End point type	Primary
End point timeframe:	
Week 18 to week 25	

End point values	Placebo	Romiplostim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20[1]	42[2]		
Units: percentage of participants				
number (confidence interval 95%)	10 (1.2 to 31.7)	52.4 (36.4 to 68)		

Notes:

[1] - Efficacy analysis set includes all randomized subjects

[2] - Efficacy analysis set includes all randomized subjects

Statistical analyses

Statistical analysis title	Primary Analysis
Statistical analysis description:	
The incidence of durable platelet response was compared by the Cochran-Mantel-Haenszel test stratified by the baseline age group. The Mantel-Haenszel common odds ratio (romiplostim vs placebo) was estimated along with its 95% confidence interval.	
Comparison groups	Placebo v Romiplostim

Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0018 [3]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	9.0497
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.896
upper limit	43.199

Notes:

[3] - p-value from Cochran-Mantel-Haenszel test stratified by baseline age group.

Secondary: Percentage of Participants with an Overall Platelet Response

End point title	Percentage of Participants with an Overall Platelet Response

End point description:

Overall platelet response is defined as either a durable platelet response or transient platelet response. Durable platelet response was defined as weekly platelet count ≥ 50 x 10^9/L for 6 or more times for Weeks 18-25 measurements. Subjects may not have a weekly response within 4 weeks after receiving any rescue medication.
Transient platelet response was defined as weekly platelet count ≥ 50 x 10^9/L for 4 or more times during Weeks 2-25 measurements but without durable platelet response. Subjects may not have a weekly response within 4 weeks after receiving any rescue medications.

End point type	Secondary

End point timeframe:

Week 2 to week 25

End point values	Placebo	Romiplostim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	42		
Units: percentage of participants				
number (confidence interval 95%)	20 (5.7 to 43.7)	71.4 (55.4 to 84.3)		

Statistical analyses

Statistical analysis title	Primary Analysis

Statistical analysis description:

The incidence of overall platelet response was compared by the Cochran-Mantel-Haenszel test stratified by the baseline age group. The Mantel-Haenszel common odds ratio (romiplostim vs placebo) was estimated along with its 95% confidence interval.

Comparison groups	Placebo v Romiplostim

Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0002 [4]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	9.0443
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.535
upper limit	32.265

Notes:

[4] - p-value from Cochran-Mantel-Haenszel test stratified by baseline age group.

Secondary: Number of Weeks with Platelet Response

End point title	Number of Weeks with Platelet Response

End point description:

Number of weeks with platelet counts ≥ 50 x 10^9/L during Weeks 2-25 measurements. Subjects may not have a weekly response within 4 weeks after receiving any rescue medications.

End point type	Secondary

End point timeframe:

Week 2 to Week 25

End point values	Placebo	Romiplostim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	42		
Units: weeks				
median (full range (min-max))	1 (0 to 22)	12 (0 to 24)		

Statistical analyses

Statistical analysis title	Primary Analysis
Comparison groups	Placebo v Romiplostim
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0004 [5]
Method	ANOVA

Notes:

[5] - p-value from Analysis of Variance with main effects (treatment and age group) model after testing for non-significant interaction (p-value ≥ 0.10).

Secondary: Percentage of Participants who Received Rescue Medication During the Treatment Period

End point title	Percentage of Participants who Received Rescue Medication During the Treatment Period

End point description:

Rescue medication is any medication (other than excluded medications) that is intended to increase platelet counts or prevent bleeding.

End point type	Secondary

End point timeframe:

24 weeks

End point values	Placebo	Romiplostim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	42		
Units: percentage of participants				
number (confidence interval 95%)	45 (23.1 to 68.5)	40.5 (25.6 to 56.7)		

Statistical analyses

Statistical analysis title	Primary Analysis

Statistical analysis description:

The incidence of rescue medication used was compared by the Cochran-Mantel-Haenszel test stratified by the baseline age group. The Mantel-Haenszel common odds ratio (romiplostim vs placebo)was estimated along with its 95% confidence interval.

Comparison groups	Placebo v Romiplostim
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7103 [6]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Odds ratio (OR)
Point estimate	0.813
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.277
upper limit	2.391

Notes:

[6] - p-value from Cochran-Mantel-Haenszel test stratified by baseline age group

Secondary: Number of Composite Bleeding Episodes

End point title	Number of Composite Bleeding Episodes

End point description:

A composite bleeding episode was defined as clinically significant bleeding events or the use of a rescue medication to prevent a clinical significant bleeding event during weeks 2 through 25 of the treatment period. A clinically significant bleeding event was defined as a Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 grade ≥ 2 bleeding event.

End point type	Secondary

End point timeframe:

25 weeks

End point values	Placebo	Romiplostim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	42		
Units: composite bleeding episodes				
arithmetic mean (standard deviation)	4 (± 6.9)	1.9 (± 4.2)		

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:

A serious adverse event is defined as an adverse event that meets at least 1 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, and/or
• other significant medical hazard.
Adverse events were graded for severity according to the CTCAE version 3.0 grading scale, where Grade 3 = moderate, Grade 4 = life-threatening and Grade 5 = fatal.
Treatment-related adverse events (TRAEs) were those assessed by the investigator as possibly related to study drug. This relationship was determined by a "yes" or "no" response to the question: "Is there a reasonable possibility that the event may have been caused by study drug?"

End point type	Secondary

End point timeframe:

From the first dose of study drug until 4 weeks after last dose; 28 weeks.

End point values	Placebo	Romiplostim		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	19	42		
Units: participants				
Any adverse event	19	41		
Serious adverse events	1	10		
Leading to discontinuation of study drug	0	0		
Leading to discontinuation from study	0	0		
Grade 3	3	6		
Grade 4	1	2		
Grade 5	0	0		
Treatment-related adverse events	5	11		
Treatment-related serious adverse events	0	1		
TRAE leading to discontinuation of study drug	0	0		

TRAE leading to discontinuation from study	0	0		
TRAE Grade 3	0	1		
TRAE Grade 4	0	0		
TRAE Grade 5	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From the first dose of study drug until 4 weeks after last dose; 28 weeks.	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Participants received weekly subcutaneous placebo for 24 weeks.	
Reporting group title	Romiplostim
Reporting group description:	
Participants received once weekly subcutaneous romiplostim for 24 weeks at a starting dose of 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.	

Serious adverse events	Placebo	Romiplostim	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 19 (5.26%)	10 / 42 (23.81%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Contusion			
subjects affected / exposed	0 / 19 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Headache			
subjects affected / exposed	0 / 19 (0.00%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Petit mal epilepsy			

subjects affected / exposed	0 / 19 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Thrombocytosis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	0 / 19 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 19 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vomiting			
subjects affected / exposed	0 / 19 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Epistaxis			
subjects affected / exposed	0 / 19 (0.00%)	2 / 42 (4.76%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Petechiae			
subjects affected / exposed	0 / 19 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			

subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nephrotic syndrome			
subjects affected / exposed	0 / 19 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchiolitis			
subjects affected / exposed	0 / 19 (0.00%)	1 / 42 (2.38%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	0 / 19 (0.00%)	1 / 42 (2.38%)	
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	19 / 19 (100.00%)	41 / 42 (97.62%)	
Vascular disorders			
Haematoma			
subjects affected / exposed	2 / 19 (10.53%)	4 / 42 (9.52%)	
occurrences (all)	5	4	
Haemorrhage			
subjects affected / exposed	2 / 19 (10.53%)	2 / 42 (4.76%)	
occurrences (all)	3	3	
Pallor			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Tooth extraction			

subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Fatigue			
subjects affected / exposed	5 / 19 (26.32%)	7 / 42 (16.67%)	
occurrences (all)	13	10	
Injection site bruising			
subjects affected / exposed	2 / 19 (10.53%)	4 / 42 (9.52%)	
occurrences (all)	6	6	
Chest pain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Nodule			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Injection site pain			
subjects affected / exposed	1 / 19 (5.26%)	4 / 42 (9.52%)	
occurrences (all)	1	4	
Localised oedema			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Oedema peripheral			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	2	0	
Peripheral swelling			
subjects affected / exposed	0 / 19 (0.00%)	4 / 42 (9.52%)	
occurrences (all)	0	4	
Pyrexia			

subjects affected / exposed	2 / 19 (10.53%)	9 / 42 (21.43%)	
occurrences (all)	2	12	
Pain			
subjects affected / exposed	1 / 19 (5.26%)	4 / 42 (9.52%)	
occurrences (all)	1	7	
Vessel puncture site bruise			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Menorrhagia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Metrorrhagia			
subjects affected / exposed	1 / 19 (5.26%)	2 / 42 (4.76%)	
occurrences (all)	2	4	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 19 (5.26%)	8 / 42 (19.05%)	
occurrences (all)	1	11	
Epistaxis			
subjects affected / exposed	10 / 19 (52.63%)	20 / 42 (47.62%)	
occurrences (all)	19	60	
Nasal congestion			
subjects affected / exposed	1 / 19 (5.26%)	5 / 42 (11.90%)	
occurrences (all)	1	5	
Nasal inflammation			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	1 / 19 (5.26%)	11 / 42 (26.19%)	
occurrences (all)	1	13	
Rhinitis allergic			

subjects affected / exposed	1 / 19 (5.26%)	2 / 42 (4.76%)	
occurrences (all)	1	2	
Rhinorrhoea			
subjects affected / exposed	2 / 19 (10.53%)	7 / 42 (16.67%)	
occurrences (all)	2	11	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 19 (5.26%)	1 / 42 (2.38%)	
occurrences (all)	1	1	
Depressed mood			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	1 / 19 (5.26%)	2 / 42 (4.76%)	
occurrences (all)	1	2	
Mood altered			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Stress			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Investigations			
Platelet count decreased			
subjects affected / exposed	3 / 19 (15.79%)	5 / 42 (11.90%)	
occurrences (all)	9	20	
Weight increased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Animal bite			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	7	0	
Animal scratch			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Arthropod bite			

subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Burns second degree			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Head injury			
subjects affected / exposed	2 / 19 (10.53%)	0 / 42 (0.00%)	
occurrences (all)	2	0	
Contusion			
subjects affected / exposed	7 / 19 (36.84%)	21 / 42 (50.00%)	
occurrences (all)	34	134	
Lip injury			
subjects affected / exposed	2 / 19 (10.53%)	0 / 42 (0.00%)	
occurrences (all)	16	0	
Muscle strain			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Laceration			
subjects affected / exposed	6 / 19 (31.58%)	2 / 42 (4.76%)	
occurrences (all)	14	5	
Post procedural haemorrhage			
subjects affected / exposed	2 / 19 (10.53%)	1 / 42 (2.38%)	
occurrences (all)	2	1	
Scratch			
subjects affected / exposed	2 / 19 (10.53%)	6 / 42 (14.29%)	
occurrences (all)	5	7	
Skin abrasion			
subjects affected / exposed	1 / 19 (5.26%)	4 / 42 (9.52%)	
occurrences (all)	1	4	
Sunburn			
subjects affected / exposed	1 / 19 (5.26%)	1 / 42 (2.38%)	
occurrences (all)	2	1	
Thermal burn			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Wound			

subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	2	0	
Tooth fracture			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Wound haemorrhage			
subjects affected / exposed	1 / 19 (5.26%)	2 / 42 (4.76%)	
occurrences (all)	1	2	
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 19 (15.79%)	4 / 42 (9.52%)	
occurrences (all)	5	5	
Headache			
subjects affected / exposed	11 / 19 (57.89%)	17 / 42 (40.48%)	
occurrences (all)	34	59	
Hypoaesthesia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Presyncope			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Syncope			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Tension headache			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Increased tendency to bruise			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Iron deficiency anaemia			
subjects affected / exposed	2 / 19 (10.53%)	1 / 42 (2.38%)	
occurrences (all)	2	1	
Anaemia			

subjects affected / exposed	1 / 19 (5.26%)	2 / 42 (4.76%)	
occurrences (all)	1	4	
Lymphadenopathy			
subjects affected / exposed	1 / 19 (5.26%)	3 / 42 (7.14%)	
occurrences (all)	2	3	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	2 / 19 (10.53%)	2 / 42 (4.76%)	
occurrences (all)	2	2	
Eye disorders			
Conjunctival haemorrhage			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Scleral discolouration			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 19 (15.79%)	4 / 42 (9.52%)	
occurrences (all)	3	6	
Constipation			
subjects affected / exposed	1 / 19 (5.26%)	5 / 42 (11.90%)	
occurrences (all)	1	6	
Diarrhoea			
subjects affected / exposed	3 / 19 (15.79%)	10 / 42 (23.81%)	
occurrences (all)	3	13	
Abdominal pain upper			
subjects affected / exposed	1 / 19 (5.26%)	5 / 42 (11.90%)	
occurrences (all)	1	6	
Dyspepsia			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Faeces discoloured			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal haemorrhage			

subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Loose tooth			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Lip haemorrhage			
subjects affected / exposed	1 / 19 (5.26%)	2 / 42 (4.76%)	
occurrences (all)	1	2	
Gingival bleeding			
subjects affected / exposed	4 / 19 (21.05%)	8 / 42 (19.05%)	
occurrences (all)	6	10	
Mouth haemorrhage			
subjects affected / exposed	4 / 19 (21.05%)	11 / 42 (26.19%)	
occurrences (all)	5	18	
Mouth ulceration			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	7 / 19 (36.84%)	8 / 42 (19.05%)	
occurrences (all)	10	9	
Oral disorder			
subjects affected / exposed	1 / 19 (5.26%)	1 / 42 (2.38%)	
occurrences (all)	1	1	
Stomatitis			
subjects affected / exposed	1 / 19 (5.26%)	3 / 42 (7.14%)	
occurrences (all)	1	5	
Tooth socket haemorrhage			
subjects affected / exposed	2 / 19 (10.53%)	1 / 42 (2.38%)	
occurrences (all)	3	1	
Vomiting			
subjects affected / exposed	4 / 19 (21.05%)	11 / 42 (26.19%)	
occurrences (all)	5	13	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	2 / 19 (10.53%)	4 / 42 (9.52%)	
occurrences (all)	3	5	

Dry skin			
subjects affected / exposed	1 / 19 (5.26%)	2 / 42 (4.76%)	
occurrences (all)	1	2	
Ecchymosis			
subjects affected / exposed	2 / 19 (10.53%)	4 / 42 (9.52%)	
occurrences (all)	2	5	
Petechiae			
subjects affected / exposed	6 / 19 (31.58%)	10 / 42 (23.81%)	
occurrences (all)	11	62	
Pruritus			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Purpura			
subjects affected / exposed	0 / 19 (0.00%)	4 / 42 (9.52%)	
occurrences (all)	0	4	
Rash			
subjects affected / exposed	2 / 19 (10.53%)	6 / 42 (14.29%)	
occurrences (all)	3	8	
Rash vesicular			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Scab			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Skin lesion			
subjects affected / exposed	1 / 19 (5.26%)	1 / 42 (2.38%)	
occurrences (all)	1	1	
Skin mass			
subjects affected / exposed	2 / 19 (10.53%)	0 / 42 (0.00%)	
occurrences (all)	3	0	
Urticaria			
subjects affected / exposed	0 / 19 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	4	
Renal and urinary disorders			
Haematuria			

subjects affected / exposed	1 / 19 (5.26%)	3 / 42 (7.14%)	
occurrences (all)	2	3	
Proteinuria			
subjects affected / exposed	1 / 19 (5.26%)	2 / 42 (4.76%)	
occurrences (all)	1	2	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 19 (15.79%)	1 / 42 (2.38%)	
occurrences (all)	3	1	
Bone pain			
subjects affected / exposed	2 / 19 (10.53%)	0 / 42 (0.00%)	
occurrences (all)	2	0	
Back pain			
subjects affected / exposed	2 / 19 (10.53%)	4 / 42 (9.52%)	
occurrences (all)	3	4	
Joint range of motion decreased			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Limb discomfort			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	1 / 19 (5.26%)	3 / 42 (7.14%)	
occurrences (all)	1	3	
Pain in extremity			
subjects affected / exposed	3 / 19 (15.79%)	5 / 42 (11.90%)	
occurrences (all)	6	7	
Temporomandibular joint syndrome			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Folliculitis			
subjects affected / exposed	1 / 19 (5.26%)	1 / 42 (2.38%)	
occurrences (all)	1	1	
Gastroenteritis			

subjects affected / exposed	0 / 19 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	3	
Oral herpes			
subjects affected / exposed	1 / 19 (5.26%)	1 / 42 (2.38%)	
occurrences (all)	1	1	
Pharyngitis streptococcal			
subjects affected / exposed	0 / 19 (0.00%)	3 / 42 (7.14%)	
occurrences (all)	0	3	
Nasopharyngitis			
subjects affected / exposed	3 / 19 (15.79%)	2 / 42 (4.76%)	
occurrences (all)	4	2	
Pneumonia			
subjects affected / exposed	2 / 19 (10.53%)	0 / 42 (0.00%)	
occurrences (all)	2	0	
Sinusitis bacterial			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Urinary tract infection			
subjects affected / exposed	1 / 19 (5.26%)	1 / 42 (2.38%)	
occurrences (all)	2	1	
Tooth abscess			
subjects affected / exposed	1 / 19 (5.26%)	0 / 42 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	5 / 19 (26.32%)	16 / 42 (38.10%)	
occurrences (all)	7	21	
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 19 (5.26%)	3 / 42 (7.14%)	
occurrences (all)	1	3	
Viral infection			
subjects affected / exposed	1 / 19 (5.26%)	1 / 42 (2.38%)	
occurrences (all)	1	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 19 (5.26%)	3 / 42 (7.14%)	
occurrences (all)	1	4	

Polydipsia subjects affected / exposed occurrences (all)	1 / 19 (5.26%) 1	0 / 42 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported