Clinical trial results:
A Patient and Investigator-blinded, Randomized, Placebo-controlled Study of LLG783 in Patients with Peripheral Artery Disease (PAD) and Intermittent Claudication

Summary

EudraCT number	2017-000706-37
Trial protocol	DE
Global end of trial date	27 December 2018

Results information

Result version number	v1 (current)
This version publication date	01 January 2020
First version publication date	01 January 2020

Trial information

Trial identification

Sponsor protocol code	CLLG783X2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03194776
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Medizinischer Infoservice (MCC), Novartis Pharma GmbH, +49 1802232300, infoservice.novartis@novartis.com
Scientific contact	Medizinischer Infoservice (MCC), Novartis Pharma GmbH, +49 1802232300, infoservice.novartis@novartis.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	27 December 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	27 December 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was evaluate the safety and tolerability of LLG783 in subjects with PAD and intermittent claudication after 16 weeks of exposure to LLG783 and to evaluate the effect of LLG783 on functional capacity after 3 months of treatment in subjects with PAD and intermittent claudication.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) E6 and Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were followed.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	20 September 2017
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	Taiwan: 2
Country: Number of subjects enrolled	United States: 4
Country: Number of subjects enrolled	Germany: 40
Worldwide total number of subjects	46
EEA total number of subjects	40

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)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	14
From 65 to 84 years	32
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 46 subjects with clinical evidence of PAD and intermittent claudication were enrolled and randomized in this study.

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	LLG783 6 mg/kg

Arm description:

Subjects received LLG783 6 milligram per kilogram (mg/kg) as intravenous (IV) infusion once every 4 weeks for a total of 4 doses over a period of 12 weeks.

Arm type	Experimental
Investigational medicinal product name	LLG783
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received LLG783 6 mg/kg as IV infusion once every 4 weeks for a total of 4 doses over a period of 12 weeks.

Arm title	Placebo

Arm description:

Subjects received placebo as IV infusion once every 4 weeks for a total of 4 doses over a period of 12 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Subjects received placebo as IV infusion once every 4 weeks for a total of 4 doses over a period of 12 weeks.

Number of subjects in period 1	LLG783 6 mg/kg	Placebo
Started	23	23
Completed	23	23

Baseline characteristics

Reporting groups	
Reporting group title	LLG783 6 mg/kg
Reporting group description:	
Subjects received LLG783 6 milligram per kilogram (mg/kg) as intravenous (IV) infusion once every 4 weeks for a total of 4 doses over a period of 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo as IV infusion once every 4 weeks for a total of 4 doses over a period of 12 weeks.	

Reporting group values	LLG783 6 mg/kg	Placebo	Total
Number of subjects	23	23	46
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	7	7	14
From 65-84 years	16	16	32
85 years and over	0	0	0
Age continuous			
Units: years			
arithmetic mean	67.0	66.3	
standard deviation	± 7.1	± 6.9	-
Gender categorical			
Units: Subjects			
Female	8	5	13
Male	15	18	33
Race			
Units: Subjects			
White	23	21	44
Asian	0	2	2
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	23	23	46
Maximum walking distance (MWD)			
MWD was determined by 6-minute walking test (6-MWT), an exercise test measuring the distance walked by a participant over a span of 6 minutes.			
Units: meters (m)			
arithmetic mean	317.3	311.3	
standard deviation	± 62.0	± 84.0	-
Pain Free Walking Distance (PWFD)			
PWFD was defined as the distance walked up to the point of onset of claudication symptoms (pain) recorded during the 6MWT.			

Units: meters (m)			
arithmetic mean	160.7	156.0	
standard deviation	± 79.4	± 86.7	-

End points

End points reporting groups

Reporting group title	LLG783 6 mg/kg
Reporting group description:	
Subjects received LLG783 6 milligram per kilogram (mg/kg) as intravenous (IV) infusion once every 4 weeks for a total of 4 doses over a period of 12 weeks.	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo as IV infusion once every 4 weeks for a total of 4 doses over a period of 12 weeks.	

Primary: Number of Subjects with Adverse Events (AEs), Drug-related AEs, Serious Adverse Events (SAEs) and Deaths

End point title	Number of Subjects with Adverse Events (AEs), Drug-related AEs, Serious Adverse Events (SAEs) and Deaths[1]
End point description:	
An AE is any untoward medical occurrence (that is, any unfavorable and unintended sign, including abnormal laboratory findings, symptom or disease) in a subject after providing written informed consent for participation in the study until the end of study visit. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product. An SAE is defined as any AE which is is fatal or life-threatening, results in persistent or significant disability/incapacity, constitutes a congenital anomaly/birth defect in offspring, requires inpatient hospitalization or prolongation of existing hospitalization and is is medically significant. Safety analysis set included all subjects that received any study treatment.	
End point type	Primary
End point timeframe:	
Up to 32 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: Only descriptive analysis was planned for this primary endpoint.

End point values	LLG783 6 mg/kg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	23	23		
Units: Subjects				
AEs	18	17		
Drug-related AEs	4	4		
SAEs	1	2		
Death	0	0		

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Maximum Walking Distance (MWD) as Assessed by 6-minute Walk Test (6MWT) at Week 16

End point title	Change from Baseline in Maximum Walking Distance (MWD) as

	Assessed by 6-minute Walk Test (6MWT) at Week 16

End point description:

MWD was assessed by the 6MWT prior to dosing was used to evaluate functional capacity of peripheral artery disease (PAD) subjects. 6MWT test included measurement of total distance walked in 6 minutes. Pharmacodynamic (PD) analysis set included all subjects with available PD data, who received any study treatment and experienced no protocol deviations with relevant impact on PD data. Here 'N' (subject analysed) signifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline, Week 16 (Day 113)

End point values	LLG783 6 mg/kg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	19		
Units: meter (m)				
least squares mean (confidence interval 80%)	19.10 (5.30 to 32.90)	36.84 (21.99 to 51.70)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Statistical analysis was done by mixed effect model repeat measurement (MMRM) model analysis.

Comparison groups	Placebo v LLG783 6 mg/kg
Number of subjects included in analysis	41
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2612 [2]
Method	two-sided test
Parameter estimate	Mean difference (final values)
Point estimate	-17.74
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-38.03
upper limit	2.55

Notes:

[2] - P-value of <= 0.2 was considered significant.

Secondary: Area Under the Serum Concentration-time Curve From Time Zero to Infinity (AUCinf)

End point title	Area Under the Serum Concentration-time Curve From Time Zero to Infinity (AUCinf)[3]

End point description:

AUCinf is defined as the area under the serum concentration-time curve from time zero to infinity. Pharmacokinetic (PK) analysis set included all subjects with at least one available valid PK concentration measurement, who received any study treatment and with no protocol deviations that impacted PK data. Here 'N' (subject analysed) signifies number of subjects evaluable for this endpoint and 'n' (number

analysed) signifies number of subjects evaluable at specified time points.
Abbreviations: mL = milliliter.

End point type	Secondary

End point timeframe:

1 hour predose and 1, 2 and 4 hours postdose on Day 1; 0 hour predose on Day 29 and 57; 0 hour predose and 1, 2 and 4 hours postdose on Day 85

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this secondary endpoint.

End point values	LLG783 6 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	20			
Units: day*microgram per mL (day*mg/mL)				
geometric mean (geometric coefficient of variation)				
Day 1 (n= 15)	2110 (± 21.1)			
Day 85 (n= 20)	4860 (± 39.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Serum Concentration-time Curve From Time Zero to the Time of the Last Quantifiable Concentration (AUClast)

End point title	Area Under the Serum Concentration-time Curve From Time Zero to the Time of the Last Quantifiable Concentration (AUClast)[4]

End point description:

AUClast is defined as the area under the serum concentration-time curve from time zero to the time of the last quantifiable concentration. PK analysis set included all subjects with at least one available valid PK concentration measurement, who received any study treatment and with no protocol deviations that impacted PK data.

End point type	Secondary

End point timeframe:

1 hour predose and 1, 2 and 4 hours postdose on Day 1; 0 hour predose on Day 29 and 57; 0 hour predose and 1, 2 and 4 hours postdose on Day 85

Notes:

[4] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this secondary endpoint.

End point values	LLG783 6 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: day*mcg/mL				
geometric mean (geometric coefficient of variation)				
Day 1	1660 (± 33.6)			
Day 85	4930 (± 38.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Serum Concentration-time Curve From Time Zero to Defined Time Point 't' (AUC[0-t])

End point title	Area Under the Serum Concentration-time Curve From Time Zero to Defined Time Point 't' (AUC[0-t])[5]

End point description:

AUC(0-t)is defined as the area under the serum concentration-time curve from time zero to time 't' where t is a defined time point after administration. PK analysis set included all subjects with at least one available valid PK concentration measurement, who received any study treatment and with no protocol deviations that impacted PK data.

End point type	Secondary

End point timeframe:

1 hour predose and 1, 2 and 4 hours postdose on Day 1; 0 hour predose on Day 29 and 57; 0 hour predose and 1, 2 and 4 hours postdose on Day 85

Notes:

[5] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this secondary endpoint.

End point values	LLG783 6 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: day*mcg/mL				
geometric mean (geometric coefficient of variation)				
Day 1	1640 (± 34.1)			
Day 85	3130 (± 34.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Area Under the Serum Concentration-time Curve From Time Zero to the End of the Dosing Interval Tau (AUCtau)

End point title	Area Under the Serum Concentration-time Curve From Time Zero to the End of the Dosing Interval Tau (AUCtau)[6]

End point description:

AUCtau is defined as the area under the serum concentration-time curve from time zero to the end of the dosing interval tau. PK analysis set included all subjects with at least one available valid PK concentration measurement, who received any study treatment and with no protocol deviations that impacted PK data.

End point type	Secondary

End point timeframe:

1 hour predose and 1, 2 and 4 hours postdose on Day 1; 0 hour predose on Day 29 and 57; 0 hour predose and 1, 2 and 4 hours postdose on Day 85

Notes:

[6] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this secondary endpoint.

End point values	LLG783 6 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: day*mcg/mL				
geometric mean (geometric coefficient of variation)				
Day 1	1640 (± 34.1)			
Day 85	3130 (± 34.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Observed Maximum Serum Concentration (Cmax) Following Drug Administration

End point title	Observed Maximum Serum Concentration (Cmax) Following Drug Administration[7]

End point description:

Cmax is defined as the observed maximum serum concentration following drug administration. PK analysis set included all subjects with at least one available valid PK concentration measurement, who received any study treatment and with no protocol deviations that impacted PK data.

End point type	Secondary

End point timeframe:

1 hour predose and 1, 2 and 4 hours postdose on Day 1; 0 hour predose on Day 29 and 57; 0 hour predose and 1, 2 and 4 hours postdose on Day 85

Notes:

[7] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this secondary endpoint.

End point values	LLG783 6 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: microgram per milliliter (mcg/mL)				
geometric mean (geometric coefficient of variation)				
Day 1	203 (± 40.0)			
Day 85	268 (± 39.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach the Maximum Concentration After Drug Administration (Tmax)

End point title	Time to Reach the Maximum Concentration After Drug Administration (Tmax)[8]

End point description:

Tmax is defined as the time to reach the maximum concentration after drug administration. PK analysis set included all subjects with at least one available valid PK concentration measurement, who received any study treatment and with no protocol deviations that impacted PK data.

End point type	Secondary

End point timeframe:

1 hour predose and 1, 2 and 4 hours postdose on Day 1; 0 hour predose on Day 29 and 57; 0 hour predose and 1, 2 and 4 hours postdose on Day 85

Notes:

[8] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis was planned for this secondary endpoint.

End point values	LLG783 6 mg/kg			
Subject group type	Reporting group			
Number of subjects analysed	23			
Units: Days				
median (full range (min-max))				
Day 1	0.0833 (0.0417 to 3.01)			
Day 85	0.0833 (0.0431 to 9.94)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Pain-free walking distance (PFWD) as Assessed by 6-minute Walk Test at Week 16

End point title	Change from Baseline in Pain-free walking distance (PFWD) as Assessed by 6-minute Walk Test at Week 16

End point description:

PFWD was defined as the distance walked up to the point of onset of claudication symptoms (pain) recorded during the 6MWT and was used to evaluate symptomatic functional capacity of PAD subjects. The PFWD was measured as the distance walked up to the time/place where the subject first experiences symptoms typical of their claudication which included pain, cramps, or other discomfort in the buttocks, thighs, calves or feet that occurs during the 6MWT exercise period. PD analysis set included all subjects with available PD data, who received any study treatment and experienced no protocol deviations with relevant impact on PD data. Here 'N' (subject analysed) signifies number of subjects evaluable for this endpoint.

End point type	Secondary

End point timeframe:

Baseline, Week 16 (Day 113)

End point values	LLG783 6 mg/kg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	22	19		
Units: meters				
least squares mean (confidence interval 80%)	44.77 (20.52 to 69.02)	57.09 (30.97 to 83.22)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups

Reporting group title	LLG783 i.v. 6 mg/kg

Reporting group description:

LLG783 i.v. 6 mg/kg

Reporting group title	Placebo

Reporting group description:

Placebo

Serious adverse events	LLG783 i.v. 6 mg/kg	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 23 (4.35%)	2 / 23 (8.70%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Small cell lung cancer			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
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			
Hypochromic anaemia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastritis haemorrhagic			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
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: 0 %

Non-serious adverse events	LLG783 i.v. 6 mg/kg	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 23 (78.26%)	16 / 23 (69.57%)	
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	2	
Peripheral arterial occlusive disease			
subjects affected / exposed	3 / 23 (13.04%)	1 / 23 (4.35%)	
occurrences (all)	3	1	
Peripheral ischaemia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Spider vein			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 23 (8.70%)	1 / 23 (4.35%)	
occurrences (all)	2	1	
Medical device site irritation			
subjects affected / exposed	3 / 23 (13.04%)	0 / 23 (0.00%)	
occurrences (all)	4	0	
Oedema peripheral			
subjects affected / exposed	2 / 23 (8.70%)	0 / 23 (0.00%)	
occurrences (all)	3	0	
Peripheral swelling			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 23 (4.35%)	1 / 23 (4.35%)	
occurrences (all)	1	1	

Cough			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Haemoptysis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Nasal congestion			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Oropharyngeal pain			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Adjustment disorder with depressed mood			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Blood creatinine increased			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Blood pressure increased			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Weight increased			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	

Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Contusion			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	2	
Limb injury			
subjects affected / exposed	1 / 23 (4.35%)	1 / 23 (4.35%)	
occurrences (all)	1	1	
Post procedural haemorrhage			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Thermal burn			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Cardiac disorders			
Atrial flutter			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Bradycardia			
subjects affected / exposed	0 / 23 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Pericardial effusion			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Sinus bradycardia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Carpal tunnel syndrome			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	

Headache			
subjects affected / exposed	2 / 23 (8.70%)	2 / 23 (8.70%)	
occurrences (all)	2	2	
Neuralgia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			
subjects affected / exposed	0 / 23 (0.00%)	2 / 23 (8.70%)	
occurrences (all)	0	2	
Sciatica			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Syncope			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Hypochromic anaemia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Lymphadenopathy			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	3 / 23 (13.04%)	1 / 23 (4.35%)	
occurrences (all)	3	1	
Nausea			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Toothache			

subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Stasis dermatitis			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Joint effusion			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	2 / 23 (8.70%)	1 / 23 (4.35%)	
occurrences (all)	2	1	
Muscle spasms			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Spinal pain			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Cystitis			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Erysipelas			

subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Infected bite			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	5 / 23 (21.74%)	4 / 23 (17.39%)	
occurrences (all)	5	4	
Paronychia			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Root canal infection			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	
Tooth abscess			
subjects affected / exposed	1 / 23 (4.35%)	0 / 23 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Iron deficiency			
subjects affected / exposed	0 / 23 (0.00%)	1 / 23 (4.35%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 July 2017	The primary purpose of this protocol amendment was to address the request from the Food and Drug Administration (FDA) to include additional safety visits two weeks after the 2nd dose and two weeks after the 3rd dose.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported