Clinical trial results:
A Randomized, Multicenter, Open-label, Parallel Group Study in Postmenopausal Women With Osteoporosis to Evaluate the Noninferiority of Subject-administered Romosozumab via Autoinjector/Pen vs Healthcare Provider-administered Romosozumab via Prefilled Syringe

Summary

EudraCT number	2017-003512-40
Trial protocol	GB PL
Global end of trial date	08 January 2020

Results information

Result version number	v1 (current)
This version publication date	21 November 2020
First version publication date	21 November 2020

Trial information

Trial identification

Sponsor protocol code	20150120

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03432533
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Amgen Inc.
Sponsor organisation address	One Amgen Center Drive, Thousand Oaks, CA, United States,
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	08 January 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the noninferiority of a 6-month treatment with romosozumab 210 mg administered subcutaneously (SC) once monthly (QM) in postmenopausal women with osteoporosis either by subject self-administration with autoinjector (AI)/pen or by healthcare provider (HCP) administration with prefilled syringe (PFS).

Protection of trial subjects:

This study was conducted in accordance with International Council for Harmonisation (ICH) Good Clinical Practice (GCP) and local regulations/guidelines. The investigator or his/her designee informed the subject of all aspects pertaining to the subject's participation in the study before any screening procedures were performed.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 February 2018
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	United States: 95
Country: Number of subjects enrolled	United Kingdom: 32
Country: Number of subjects enrolled	Poland: 156
Worldwide total number of subjects	283
EEA total number of subjects	188

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)	74

From 65 to 84 years	197
85 years and over	12

Subject disposition

Recruitment

Recruitment details:

Participants were enrolled at 36 centers in Poland, United Kingdom, and United States.

Pre-assignment

Screening details:

Participants were randomized in a 1:1 ratio.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Romosozumab 210 mg QM: PFS

Arm description:

During the open-label treatment period, participants received 210 mg romosozumab subcutaneously (SC) once a month (QM) by health care provider (HCP) administration with pre-filled syringe (PFS).

Arm type	Experimental
Investigational medicinal product name	romosozumab
Investigational medicinal product code	AMG785
Other name	Evenity
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subconjunctival use, Subcutaneous use

Dosage and administration details:

210 mg romosozumab SC QM by HCP administration with 2 PFS

Arm title	Romosozumab 210 mg QM: AI/Pen

Arm description:

During the open-label treatment period, participants received 210 mg romosozumab SC QM by self-administration with autoinjector (AI)/pen.

Arm type	Experimental
Investigational medicinal product name	romosozumab
Investigational medicinal product code	AMG785
Other name	Evenity
Pharmaceutical forms	Solution for injection in pre-filled pen
Routes of administration	Subcutaneous use

Dosage and administration details:

210 mg romosozumab SC QM by self-administration with 2 AI/Pens

Number of subjects in period 1	Romosozumab 210 mg QM: PFS	Romosozumab 210 mg QM: AI/Pen
Started	141	142
Completed 6-Month Treatment Period	136	137
Completed	126	131
Not completed	15	11
Consent withdrawn by subject	14	9
Lost to follow-up	1	2

Baseline characteristics

Reporting groups	
Reporting group title	Romosozumab 210 mg QM: PFS
Reporting group description:	
During the open-label treatment period, participants received 210 mg romosozumab subcutaneously (SC) once a month (QM) by health care provider (HCP) administration with pre-filled syringe (PFS).	
Reporting group title	Romosozumab 210 mg QM: AI/Pen
Reporting group description:	
During the open-label treatment period, participants received 210 mg romosozumab SC QM by self-administration with autoinjector (AI)/pen.	

Reporting group values	Romosozumab 210 mg QM: PFS	Romosozumab 210 mg QM: AI/Pen	Total
Number of subjects	141	142	283
Age categorical			
Units: Subjects			
Age Continuous			
Units: years			
arithmetic mean	70.3	69.5	
standard deviation	± 7.1	± 8.4	-
Sex: Female, Male			
Units:			
Female	141	142	283
Male	0	0	0
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	3	1	4
Not Hispanic or Latino	138	141	279
Unknown or Not Reported	0	0	0
Participants With Pre-Existing Anti-Romosozumab Antibodies			
Number of participants with pre-existing antibodies, including those who were binding antibody positive and those who were neutralizing antibody positive at or before baseline (BL).			
Units: Subjects			
Binding Antibody Positive at or Before BL	3	0	3
Neutralizing Antibody Positive at or Before BL	0	0	0
Binding Antibody Negative at or Before BL	138	142	280
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	1	1	2
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	1	2
White	139	140	279
More than one race	0	0	0
Unknown or Not Reported	0	0	0

Lumbar Spine Bone Mineral Density (BMD) T-Score			
The T-score is the BMD at the site when compared to that of a healthy thirty-year-old of the same sex. Lower scores (more negative) mean lower bone density. Normal is a T-score of −1.0 or higher; Osteopenia is defined as between −1.0 and −2.5, meaning below-normal bone density without full osteoporosis; Osteoporosis is defined as −2.5 or lower, meaning a bone density that is two and a half standard deviations below the mean of a thirty-year-old man/woman.			
Units: T-score			
arithmetic mean	-2.69	-2.85	
standard deviation	± 1.03	± 1.00	-
Total Hip BMD T-Score			
The T-score is the BMD at the site when compared to that of a healthy thirty-year-old of the same sex. Lower scores (more negative) mean lower bone density. Normal is a T-score of −1.0 or higher; Osteopenia is defined as between −1.0 and −2.5, meaning below-normal bone density without full osteoporosis; Osteoporosis is defined as −2.5 or lower, meaning a bone density that is two and a half standard deviations below the mean of a thirty-year-old man/woman.			
Units: T-score			
arithmetic mean	-2.29	-2.30	
standard deviation	± 0.73	± 0.77	-
Femoral Neck BMD T-Score			
The T-score is the BMD at the site when compared to that of a healthy thirty-year-old of the same sex. Lower scores (more negative) mean lower bone density. Normal is a T-score of −1.0 or higher; Osteopenia is defined as between −1.0 and −2.5, meaning below-normal bone density without full osteoporosis; Osteoporosis is defined as −2.5 or lower, meaning a bone density that is two and a half standard deviations below the mean of a thirty-year-old man/woman.			
Units: T-score			
arithmetic mean	-2.54	-2.49	
standard deviation	± 0.63	± 0.65	-

End points

End points reporting groups

Reporting group title	Romosozumab 210 mg QM: PFS
Reporting group description:	
During the open-label treatment period, participants received 210 mg romosozumab subcutaneously (SC) once a month (QM) by health care provider (HCP) administration with pre-filled syringe (PFS).	
Reporting group title	Romosozumab 210 mg QM: AI/Pen
Reporting group description:	
During the open-label treatment period, participants received 210 mg romosozumab SC QM by self-administration with autoinjector (AI)/pen.	

Primary: Percent Change From Baseline in Lumbar Spine BMD at Month 6

End point title	Percent Change From Baseline in Lumbar Spine BMD at Month 6
End point description:	
Percent change from baseline in BMD at the lumbar spine as measured by dual-energy x-ray absorptiometry (DXA).	
End point type	Primary
End point timeframe:	
Baseline, Month 6	

End point values	Romosozumab 210 mg QM: PFS	Romosozumab 210 mg QM: AI/Pen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	134		
Units: percent change				
least squares mean (standard error)	9.2 (± 0.4)	9.0 (± 0.5)		

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Comparison groups	Romosozumab 210 mg QM: PFS v Romosozumab 210 mg QM: AI/Pen
Number of subjects included in analysis	269
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.84
Method	ANCOVA
Parameter estimate	LS Mean Difference
Point estimate	-0.1

Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.3
upper limit	1
Variability estimate	Standard error of the mean
Dispersion value	0.6

Secondary: Percent Change From Baseline in Total Hip BMD at Month 6

End point title	Percent Change From Baseline in Total Hip BMD at Month 6
End point description:	
Percent change from baseline in BMD for total hip as measured by DXA.	
End point type	Secondary
End point timeframe:	
Baseline, Month 6	

End point values	Romosozumab 210 mg QM: PFS	Romosozumab 210 mg QM: AI/Pen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	134		
Units: percent change				
least squares mean (standard error)	3.7 (± 0.6)	3.6 (± 0.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change From Baseline in Femoral Neck BMD at Month 6

End point title	Percent Change From Baseline in Femoral Neck BMD at Month 6
End point description:	
Percent change from baseline in BMD at femoral neck as measured by DXA.	
End point type	Secondary
End point timeframe:	
Baseline, Month 6	

End point values	Romosozumab 210 mg QM: PFS	Romosozumab 210 mg QM: AI/Pen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	135	134		
Units: percent change				
least squares mean (standard error)	3.4 (± 0.7)	3.6 (± 0.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment Emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs), Device-Related AEs, Discontinuations Due to AEs, and Deaths

End point title	Number of Participants With Treatment Emergent Adverse Events (TEAEs), Serious Adverse Events (SAEs), Device-Related AEs, Discontinuations Due to AEs, and Deaths

End point description:

AE: any untoward medical occurrence irrespective of a causal relationship with the study treatment. SAE: any untoward medical occurrence that meets at least 1 of the following criteria: results in death; is immediately life-threatening; requires in-patient hospitalization or prolongation of existing hospitalization; results in persistent or significant disability/incapacity; is a congenital anomaly/birth defect; is a medically important serious event. Adverse device effect: any AE related to the use of a combination product or medical device. TEAEs are those AEs occurring after first dose of study drug.

End point type	Secondary

End point timeframe:

up to Month 9 (-7/+3 days)

End point values	Romosozumab 210 mg QM: PFS	Romosozumab 210 mg QM: AI/Pen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	142		
Units: participants				
TEAEs: All	94	96		
TEAEs: SAEs	7	4		
TEAEs: Leading to Study Drug Discontinuation (DC)	7	15		
TEAEs: Fatal	0	0		
Treatment-Related (TR) TEAEs: All	38	59		
TR TEAEs: SAEs	0	0		
TR TEAEs: Leading to Study Drug DC	6	10		
TR TEAEs: Fatal	0	0		
Device-Related (DR) TEAEs: All	18	30		
DR TEAEs: SAEs	0	0		
DR TEAEs: Leading to Study Drug DC	0	5		
DR TEAEs: Fatal	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants Developing Anti-Romosozumab Antibodies

End point title	Number of Participants Developing Anti-Romosozumab Antibodies

End point description:

Participants with a negative or no result at baseline (BL) developing anti-romosozumab antibodies postbaseline, including those who were binding antibody-positive or neutralizing antibody-positive postbaseline. 'Transient' positive results are those with a negative result at the participant's last time point tested within the study period.

End point type	Secondary

End point timeframe:

up to Month 9 (-7/+3 days)

End point values	Romosozumab 210 mg QM: PFS	Romosozumab 210 mg QM: AI/Pen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	139	142		
Units: participants				
Binding Antibody Positive Post-BL	21	22		
Transient Binding Antibody Positive Post-BL	6	3		
Neutralizing Antibody Positive Post-BL	5	4		
Transient Neutralizing Antibody Positive Post-BL	0	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: up to Month 9 (-7/+3 days)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups	
Reporting group title	Romosozumab 210 mg SC QM by PFS
Reporting group description: During the open-label treatment period, participants received 210 mg romosozumab subcutaneously (SC) once a month (QM) by health care provider (HCP) administration with pre-filled syringe (PFS).	
Reporting group title	Romosozumab 210 mg SC QM by AI/Pen
Reporting group description: During the open-label treatment period, participants received 210 mg romosozumab SC QM by self-administration with autoinjector (AI)/pen.	

Serious adverse events	Romosozumab 210 mg SC QM by PFS	Romosozumab 210 mg SC QM by AI/Pen	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 141 (4.96%)	4 / 142 (2.82%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Glioblastoma			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Forearm fracture			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Humerus fracture			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 141 (0.71%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Colitis ischaemic			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			

subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Clostridium difficile infection			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Romosozumab 210 mg SC QM by PFS	Romosozumab 210 mg SC QM by AI/Pen	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	92 / 141 (65.25%)	95 / 142 (66.90%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lipoma			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Meningioma			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Seborrhoeic keratosis			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Hot flush			
subjects affected / exposed	2 / 141 (1.42%)	1 / 142 (0.70%)	
occurrences (all)	2	1	
Hypertension			

subjects affected / exposed	3 / 141 (2.13%)	1 / 142 (0.70%)	
occurrences (all)	3	1	
Hypotension			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Vasculitis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Injection site erythema			
subjects affected / exposed	25 / 141 (17.73%)	35 / 142 (24.65%)	
occurrences (all)	49	69	
Injection site pain			
subjects affected / exposed	14 / 141 (9.93%)	21 / 142 (14.79%)	
occurrences (all)	20	34	
Injection site swelling			
subjects affected / exposed	11 / 141 (7.80%)	23 / 142 (16.20%)	
occurrences (all)	13	43	
Asthenia			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Chest pain			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Chills			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Cyst			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Exercise tolerance decreased			

subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	1 / 141 (0.71%)	2 / 142 (1.41%)	
occurrences (all)	1	4	
Influenza like illness			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Injection site bruising			
subjects affected / exposed	1 / 141 (0.71%)	5 / 142 (3.52%)	
occurrences (all)	2	7	
Injection site discolouration			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Injection site extravasation			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Injection site haemorrhage			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Injection site hypersensitivity			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Injection site hypertrophy			
subjects affected / exposed	1 / 141 (0.71%)	1 / 142 (0.70%)	
occurrences (all)	1	1	
Injection site induration			
subjects affected / exposed	2 / 141 (1.42%)	2 / 142 (1.41%)	
occurrences (all)	7	2	
Injection site irritation			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Injection site nodule			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Injection site oedema			

subjects affected / exposed	2 / 141 (1.42%)	4 / 142 (2.82%)	
occurrences (all)	2	7	
Injection site pruritus			
subjects affected / exposed	6 / 141 (4.26%)	7 / 142 (4.93%)	
occurrences (all)	8	15	
Injection site rash			
subjects affected / exposed	0 / 141 (0.00%)	2 / 142 (1.41%)	
occurrences (all)	0	2	
Injection site reaction			
subjects affected / exposed	3 / 141 (2.13%)	2 / 142 (1.41%)	
occurrences (all)	4	3	
Injection site urticaria			
subjects affected / exposed	0 / 141 (0.00%)	2 / 142 (1.41%)	
occurrences (all)	0	2	
Injection site warmth			
subjects affected / exposed	2 / 141 (1.42%)	3 / 142 (2.11%)	
occurrences (all)	2	6	
Malaise			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Mass			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	2	
Non-cardiac chest pain			
subjects affected / exposed	1 / 141 (0.71%)	1 / 142 (0.70%)	
occurrences (all)	1	1	
Oedema peripheral			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Pain			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	2	
Peripheral swelling			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Pyrexia			

subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Breast cyst			
subjects affected / exposed	0 / 141 (0.00%)	2 / 142 (1.41%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	0 / 141 (0.00%)	3 / 142 (2.11%)	
occurrences (all)	0	3	
Dysphonia			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	2	
Dyspnoea			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Nasal congestion			
subjects affected / exposed	1 / 141 (0.71%)	1 / 142 (0.70%)	
occurrences (all)	1	1	
Pulmonary fibrosis			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Rhinitis allergic			
subjects affected / exposed	3 / 141 (2.13%)	0 / 142 (0.00%)	
occurrences (all)	3	0	
Rhinorrhoea			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 141 (0.71%)	1 / 142 (0.70%)	
occurrences (all)	1	1	
Insomnia			
subjects affected / exposed	3 / 141 (2.13%)	2 / 142 (1.41%)	
occurrences (all)	3	2	
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	2 / 141 (1.42%)	0 / 142 (0.00%)	
occurrences (all)	2	0	
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Blood creatinine increased			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Blood urea increased			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Chest X-ray abnormal			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Anaemia postoperative			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Arthropod bite			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Bone contusion			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Cataract operation complication			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Contusion			
subjects affected / exposed	3 / 141 (2.13%)	1 / 142 (0.70%)	
occurrences (all)	4	1	
Epicondylitis			

subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Facial bones fracture			
subjects affected / exposed	1 / 141 (0.71%)	1 / 142 (0.70%)	
occurrences (all)	1	1	
Fall			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Femur fracture			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Fibula fracture			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Foot fracture			
subjects affected / exposed	2 / 141 (1.42%)	2 / 142 (1.41%)	
occurrences (all)	2	2	
Hand fracture			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Humerus fracture			
subjects affected / exposed	1 / 141 (0.71%)	1 / 142 (0.70%)	
occurrences (all)	1	1	
Post procedural complication			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Post-traumatic pain			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Procedural pain			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Radius fracture			
subjects affected / exposed	2 / 141 (1.42%)	0 / 142 (0.00%)	
occurrences (all)	2	0	
Spinal column injury			

subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Tooth injury			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Cardiac disorders			
Bundle branch block right			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Myocardial ischaemia			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Palpitations			
subjects affected / exposed	2 / 141 (1.42%)	0 / 142 (0.00%)	
occurrences (all)	2	0	
Ventricular pre-excitation			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	3 / 141 (2.13%)	9 / 142 (6.34%)	
occurrences (all)	4	13	
Dementia			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	2 / 141 (1.42%)	1 / 142 (0.70%)	
occurrences (all)	2	1	
Paraesthesia			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Post herpetic neuralgia			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Sciatica			

subjects affected / exposed	1 / 141 (0.71%)	1 / 142 (0.70%)	
occurrences (all)	1	1	
Transient ischaemic attack			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Leukocytosis			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Leukopenia			
subjects affected / exposed	4 / 141 (2.84%)	0 / 142 (0.00%)	
occurrences (all)	4	0	
Neutropenia			
subjects affected / exposed	2 / 141 (1.42%)	2 / 142 (1.41%)	
occurrences (all)	2	2	
Normocytic anaemia			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	2	
Ear and labyrinth disorders			
Ear congestion			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Tinnitus			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Vertigo			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Eye disorders			
Age-related macular degeneration			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Blepharitis			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Cataract			

subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Dry eye			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Entropion			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Macular degeneration			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Ocular hyperaemia			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Swelling of eyelid			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Vision blurred			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Visual impairment			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Abdominal pain			
subjects affected / exposed	1 / 141 (0.71%)	2 / 142 (1.41%)	
occurrences (all)	1	2	
Abdominal pain lower			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Abdominal pain upper			
subjects affected / exposed	0 / 141 (0.00%)	3 / 142 (2.11%)	
occurrences (all)	0	3	

Colitis			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	1 / 141 (0.71%)	2 / 142 (1.41%)	
occurrences (all)	1	2	
Dental cyst			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Diaphragmatic hernia			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Diarrhoea			
subjects affected / exposed	5 / 141 (3.55%)	1 / 142 (0.70%)	
occurrences (all)	5	1	
Diverticulum intestinal			
subjects affected / exposed	0 / 141 (0.00%)	2 / 142 (1.41%)	
occurrences (all)	0	2	
Dry mouth			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Gastritis			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 141 (0.71%)	2 / 142 (1.41%)	
occurrences (all)	1	2	
Gingival pain			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Hiatus hernia			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Irritable bowel syndrome			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	

Large intestine polyp			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Nausea			
subjects affected / exposed	2 / 141 (1.42%)	2 / 142 (1.41%)	
occurrences (all)	2	2	
Oesophageal ulcer			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Oral mucosal blistering			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	2	
Stomatitis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Toothache			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	0 / 141 (0.00%)	2 / 142 (1.41%)	
occurrences (all)	0	2	
Hepatobiliary disorders			
Hypertransaminasaemia			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Decubitus ulcer			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Dermal cyst			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Dermatitis			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Dermatitis allergic			

subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Dry skin			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	1 / 141 (0.71%)	1 / 142 (0.70%)	
occurrences (all)	1	3	
Pruritus generalised			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Rash			
subjects affected / exposed	4 / 141 (2.84%)	1 / 142 (0.70%)	
occurrences (all)	4	1	
Rash pruritic			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Swelling face			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Micturition urgency			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Renal cyst			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Renal failure			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Urinary incontinence			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Endocrine disorders			
Hypothyroidism			

subjects affected / exposed	2 / 141 (1.42%)	0 / 142 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	7 / 141 (4.96%)	9 / 142 (6.34%)	
occurrences (all)	8	12	
Arthritis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Back pain			
subjects affected / exposed	2 / 141 (1.42%)	3 / 142 (2.11%)	
occurrences (all)	2	4	
Bone pain			
subjects affected / exposed	3 / 141 (2.13%)	1 / 142 (0.70%)	
occurrences (all)	3	1	
Bursitis			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Muscle spasms			
subjects affected / exposed	1 / 141 (0.71%)	2 / 142 (1.41%)	
occurrences (all)	1	2	
Muscular weakness			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal pain			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Musculoskeletal stiffness			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	2 / 141 (1.42%)	1 / 142 (0.70%)	
occurrences (all)	2	1	
Neck pain			

subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Nodal osteoarthritis			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Osteoarthritis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Pain in extremity			
subjects affected / exposed	4 / 141 (2.84%)	3 / 142 (2.11%)	
occurrences (all)	4	5	
Plantar fasciitis			
subjects affected / exposed	2 / 141 (1.42%)	0 / 142 (0.00%)	
occurrences (all)	2	0	
Rheumatoid arthritis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Spinal osteoarthritis			
subjects affected / exposed	2 / 141 (1.42%)	1 / 142 (0.70%)	
occurrences (all)	2	1	
Spinal pain			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Spondylitis			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	15 / 141 (10.64%)	10 / 142 (7.04%)	
occurrences (all)	16	10	
Upper respiratory tract infection			
subjects affected / exposed	2 / 141 (1.42%)	8 / 142 (5.63%)	
occurrences (all)	2	8	
Bacterial vulvovaginitis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	

Bronchitis			
subjects affected / exposed	4 / 141 (2.84%)	6 / 142 (4.23%)	
occurrences (all)	4	8	
Cystitis			
subjects affected / exposed	3 / 141 (2.13%)	0 / 142 (0.00%)	
occurrences (all)	3	0	
Ear infection			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Furuncle			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	1 / 141 (0.71%)	1 / 142 (0.70%)	
occurrences (all)	1	1	
Genital herpes			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Herpes virus infection			
subjects affected / exposed	0 / 141 (0.00%)	2 / 142 (1.41%)	
occurrences (all)	0	2	
Herpes zoster			
subjects affected / exposed	1 / 141 (0.71%)	1 / 142 (0.70%)	
occurrences (all)	1	1	
Hordeolum			
subjects affected / exposed	1 / 141 (0.71%)	1 / 142 (0.70%)	
occurrences (all)	1	1	
Influenza			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Laryngitis			
subjects affected / exposed	1 / 141 (0.71%)	1 / 142 (0.70%)	
occurrences (all)	1	1	
Lower respiratory tract infection			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	

Lung abscess			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Oral herpes			
subjects affected / exposed	2 / 141 (1.42%)	1 / 142 (0.70%)	
occurrences (all)	2	1	
Pharyngitis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Pharyngitis streptococcal			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Pneumonia			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Respiratory tract infection			
subjects affected / exposed	2 / 141 (1.42%)	2 / 142 (1.41%)	
occurrences (all)	2	2	
Rhinitis			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	2 / 141 (1.42%)	1 / 142 (0.70%)	
occurrences (all)	2	1	
Tonsillitis			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Tooth infection			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Tooth abscess			
subjects affected / exposed	1 / 141 (0.71%)	1 / 142 (0.70%)	
occurrences (all)	1	1	
Urethritis			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	

Urinary tract infection			
subjects affected / exposed	4 / 141 (2.84%)	4 / 142 (2.82%)	
occurrences (all)	4	4	
Urinary tract infection bacterial			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Viral infection			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Viral labyrinthitis			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Dehydration			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Glucose tolerance impaired			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Hyperglycaemia			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Hyperlipidaemia			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Hypoalbuminaemia			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Hypocalcaemia			
subjects affected / exposed	1 / 141 (0.71%)	1 / 142 (0.70%)	
occurrences (all)	1	1	
Hypokalaemia			

subjects affected / exposed	1 / 141 (0.71%)	2 / 142 (1.41%)	
occurrences (all)	1	2	
Hyponatraemia			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Malnutrition			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Type 2 diabetes mellitus			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	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