Clinical trial results:
A PHASE 2, MULTICENTER, RANDOMIZED, ACTIVE-CONTROLLED, PARALLEL-GROUP, DOSE-FINDING AND SAFETY STUDY OF RECOMBINANT HUMAN BONE MORPHOGENETIC PROTEIN-2 (RHBMP 2)/CALCIUM PHOSPHATE MATRIX (CPM) IN SUBJECTS WITH DECREASED BONE MINERAL DENSITY

Summary

EudraCT number	2007-007456-34
Trial protocol	ES BE PL FI NL
Global end of trial date	24 April 2015

Results information

Result version number	v1 (current)
This version publication date	31 July 2016
First version publication date	31 July 2016

Trial information

Trial identification

Sponsor protocol code	3100N0-2213-WW

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00752557
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Pfizer, Inc.
Sponsor organisation address	235 East 42nd Street,, New York, United States, 10017
Public contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., +1 800 718 1021, ClinicalTrials.gov_Inquiries@pfizer.com
Scientific contact	Pfizer ClinicalTrials.gov Call Center, Pfizer, Inc., +1 800 718 1021, ClinicalTrials.gov_Inquiries@pfizer.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	31 August 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 April 2015
Global end of trial reached?	Yes
Global end of trial date	24 April 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study was to show increased bone mineral density (BMD) of the proximal femur (total hip [TH] BMD) after injection of rhBMP-2/CPM (either 1 mg/mL) as an adjunct to systemic osteoporosis (OP) therapy. To assess the primary objective, BMD was measured by dual-energy x-ray absorptiometry (DXA) every 3 months from 6 to 12 months.

Protection of trial subjects:

This study was conducted in compliance with the ethical principles derived from the Declaration of Helsinki and in compliance with all International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial participants.

Background therapy:

Regardless of treatment group assignment, bisphosphonate, calcium, and vitamin D were provided to all study participants as background therapy to provide adequate protection against osteoporosis.

Evidence for comparator: -

Actual start date of recruitment	03 December 2008
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	60 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 4
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	United States: 41
Worldwide total number of subjects	46
EEA total number of subjects	5

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	45
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 10 centers in the United States of America, Belgium, and Poland.

Pre-assignment

Screening details:

Treatments were stratified by previous OP therapy regardless of rhBMP-2/CPM treatment assignment; bisphosphonate, calcium, vitamin D were provided to all participants as background concomitant OP therapy. Due to early termination of participant enrollment, efficacy analyses were not performed as the study never reached its intended sample size.

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

Blinding implementation details:

The trial was designed to allow for the Sponsor to be fully unblinded throughout the trial. To minimize the selection bias, the trial used a centralized, automated randomization procedure. Separate randomization lists were available for each randomization strata (Naïve participants and those with previous exposure to system OP therapy). To further reduce selection bias, randomization was carried out at the level of the hip, systematically and prospectively designated by the randomization schema.

Arms

Are arms mutually exclusive?	Yes
Arm title	Standard of Care Control

Arm description:

Participants had received systemic osteoporosis therapy with an oral bisphosphonate plus supplemental calcium, and vitamin D as prescribed by the study physician.

Arm type	Active comparator
Investigational medicinal product name	Oral bisphosphonate therapy, Calcium and Vitamin D
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Oral bisphosphonate plus supplemental calcium, and vitamin D as prescribed by the study physician.

Arm title	rhBMP-2/CPM 1.0 mg/mL

Arm description:

Participants had received 1 mg/mL rhBMP 2/CPM administered via intraosseous injection administered percutaneously to the proximal femur. Participants in treatment groups additionally received SOC treatment for OP.

Arm type	Experimental
Investigational medicinal product name	rhBMP-2/CPM (Dibotermin alfa)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intraosseous use

Dosage and administration details:

1 mg/mL rhBMP-2/CPM administered via intraosseous injection administered percutaneously to the proximal femur.

Arm title	rhBMP-2/CPM 2.0 mg/mL

Arm description:

Participants had received 2 mg/mL rhBMP 2/CPM administered via intraosseous injection administered percutaneously to the proximal femur. Participants in both injected treatment groups additionally received SOC treatment for OP.

Arm type	Experimental
Investigational medicinal product name	rhBMP-2/CPM (Dibotermin alfa)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intraosseous use

Dosage and administration details:

2 mg/mL rhBMP-2/CPM administered via intraosseous injection administered percutaneously to the proximal femur.

Number of subjects in period 1	Standard of Care Control	rhBMP-2/CPM 1.0 mg/mL	rhBMP-2/CPM 2.0 mg/mL
Started	17	15	14
Completed	12	11	11
Not completed	5	4	3
Consent withdrawn by subject	4	3	2
Lost to follow-up	1	-	1
Unspecified reasons	-	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Standard of Care Control
Reporting group description:	
Participants had received systemic osteoporosis therapy with an oral bisphosphonate plus supplemental calcium, and vitamin D as prescribed by the study physician.	
Reporting group title	rhBMP-2/CPM 1.0 mg/mL
Reporting group description:	
Participants had received 1 mg/mL rhBMP 2/CPM administered via intraosseous injection administered percutaneously to the proximal femur. Participants in treatment groups additionally received SOC treatment for OP.	
Reporting group title	rhBMP-2/CPM 2.0 mg/mL
Reporting group description:	
Participants had received 2 mg/mL rhBMP 2/CPM administered via intraosseous injection administered percutaneously to the proximal femur. Participants in both injected treatment groups additionally received SOC treatment for OP.	

Reporting group values	Standard of Care Control	rhBMP-2/CPM 1.0 mg/mL	rhBMP-2/CPM 2.0 mg/mL
Number of subjects	17	15	14
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)	0	0	0
From >= 65 years	17	15	14
Age Continuous | Units: years			
arithmetic mean	73.35	75.93	73.21
standard deviation	± 5.454	± 5.271	± 5.041
Gender, Male/Female Units: Participants			
Female	17	15	14
Male	0	0	0

Reporting group values	Total		
Number of subjects	46		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	0		
From >= 65 years	46		
Age Continuous |			
Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female			
Units: Participants			
Female	46		
Male	0		

End points

End points reporting groups

Reporting group title	Standard of Care Control
Reporting group description:	
Participants had received systemic osteoporosis therapy with an oral bisphosphonate plus supplemental calcium, and vitamin D as prescribed by the study physician.	
Reporting group title	rhBMP-2/CPM 1.0 mg/mL
Reporting group description:	
Participants had received 1 mg/mL rhBMP 2/CPM administered via intraosseous injection administered percutaneously to the proximal femur. Participants in treatment groups additionally received SOC treatment for OP.	
Reporting group title	rhBMP-2/CPM 2.0 mg/mL
Reporting group description:	
Participants had received 2 mg/mL rhBMP 2/CPM administered via intraosseous injection administered percutaneously to the proximal femur. Participants in both injected treatment groups additionally received SOC treatment for OP.	

Primary: Change from Baseline in Bone Mineral Density (BMD) measured by Dual-Energy X-ray Absorptiometry (DXA)

End point title	Change from Baseline in Bone Mineral Density (BMD) measured by Dual-Energy X-ray Absorptiometry (DXA)[1]
End point description:	
Evaluating local changes (expected increases) in BMD after administration of rhBMP-2/CPM, compared to those observed with systemic osteoporosis therapy alone. Alternatively, if changes in the total area surrounding the proximal femur are observed, bone mineral content (BMC) may instead be applied for the primary measure. BMD is defined as a derived measure of bone density, generated by dividing the bone mineral content value obtained from a bone densitometry technique (for example, DXA) by the total area of the region scanned. Due to early termination of participant enrollment, mainly descriptive statistics were provided, and no statistical tests were performed.	
End point type	Primary
End point timeframe:	
12 months post dose	

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: No inferential statistical analysis was done.

End point values	Standard of Care Control	rhBMP-2/CPM 1.0 mg/mL	rhBMP-2/CPM 2.0 mg/mL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	14	12	14	
Units: g/cm2				
arithmetic mean (standard deviation)				
Total hip	-0.0026 (± 0.018)	0.1299 (± 0.045)	0.1196 (± 0.063)	
Intertrochanter	-0.0029 (± 0.02)	0.1063 (± 0.066)	0.1192 (± 0.063)	
Trochanter	-0.0091 (± 0.023)	0.1197 (± 0.066)	0.0869 (± 0.073)	
Femoral neck	0.0058 (± 0.021)	0.2408 (± 0.111)	0.212 (± 0.117)	

Statistical analyses

No statistical analyses for this end point

Primary: Time course distribution of volumetric BMD for the Hip Under Study (HUS) for total hip

End point title	Time course distribution of volumetric BMD for the Hip Under Study (HUS) for total hip[2]

End point description:

Evaluating local changes (expected increases) in BMD after administration of rhBMP-2/CPM, compared to those observed with systemic osteoporosis therapy alone. Alternatively, if changes in the total area surrounding the proximal femur are observed, bone mineral content (BMC) may instead be applied for the primary measure.

End point type	Primary

End point timeframe:

12 months with Follow-Up ±14 days

Notes:

[2] - 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: No inferential statistical analysis was done.

End point values	Standard of Care Control	rhBMP-2/CPM 1.0 mg/mL	rhBMP-2/CPM 2.0 mg/mL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	11	14	
Units: mg/cm3				
arithmetic mean (standard deviation)				
Cortical + Sub-Cortical	136.8 (± 16.91)	165.6 (± 18.37)	151.6 (± 26.07)	
Peeled Trabecular	45.1 (± 16.02)	77.8 (± 23.07)	88.4 (± 37.63)	
Integral	181.9 (± 20.6)	243.4 (± 31.04)	240 (± 45.31)	

Statistical analyses

No statistical analyses for this end point

Primary: Timecourse Distribution of Volumetric Bone Mineral Density (BMD) for the Hip Under Study (HUS). Volume of Interest: Femoral Neck

End point title	Timecourse Distribution of Volumetric Bone Mineral Density (BMD) for the Hip Under Study (HUS). Volume of Interest: Femoral Neck[3]

End point description:

Evaluating local changes (expected increases) in BMD after administration of rhBMP-2/CPM, compared to those observed with systemic osteoporosis therapy alone. Alternatively, if changes in the total area surrounding the proximal femur are observed, bone mineral content (BMC) may instead be applied for the primary measure.

End point type	Primary

End point timeframe:

12 months with Follow-Up ±14 days

Notes:

[3] - 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: No inferential statistical analysis was done.

End point values	Standard of Care Control	rhBMP-2/CPM 1.0 mg/mL	rhBMP-2/CPM 2.0 mg/mL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	13	11	14	
Units: mg/cm3				
arithmetic mean (standard deviation)				
Cortical +Sub Cortical	144.3 (± 16.81)	166.3 (± 31.06)	164.4 (± 29.37)	
Peeled Trabecular	61.1 (± 14.39)	165 (± 59.13)	159.3 (± 38.97)	
Integral	205.4 (± 23.02)	331.3 (± 73.99)	323.7 (± 58.96)	

Statistical analyses

No statistical analyses for this end point

Secondary: Summary of Cortical Thickness and Trabecular Bone Volume Calculated by Quantitative Computed Tomography (vQTC)

End point title	Summary of Cortical Thickness and Trabecular Bone Volume Calculated by Quantitative Computed Tomography (vQTC)

End point description:

Measurement of cortical thickness in various regions of interest (ROIs) in the femoral neck, proximal shaft, and individual trochanters and quantification of trabecular bone volume in ROIs

End point type	Secondary

End point timeframe:

24 months

End point values	Standard of Care Control	rhBMP-2/CPM 1.0 mg/mL	rhBMP-2/CPM 2.0 mg/mL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	5	7	6	
Units: mg/cm3				
arithmetic mean (standard deviation)				
Cortical Thickness	2.5782 (± 0.16805)	2.4259 (± 0.24267)	2.5128 (± 0.17484)	
Trabecular Bone Volume	0 (± 0)	4.7073 (± 2.405)	4.2205 (± 1.63904)	

Statistical analyses

No statistical analyses for this end point

Secondary: Number participant responses to Injectability Questionnaire Injected Population

End point title	Number participant responses to Injectability Questionnaire Injected Population[4]

End point description:

Investigator documents preparation of the study medication evaluates injectability and product placement relative to desired location (for participants in active treatment groups). Surgeon performing the injection had to complete the questionnaire that evaluates ease of preparing the study medication, ability to administer study medication, and ability for the study medication to remain in the location it was administered.

End point type	Secondary

End point timeframe:

Participants were monitored after treatment administration (dosing period)

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 descriptive statistics was done for the reporting arm standard of care control.

End point values	rhBMP-2/CPM 1.0 mg/mL	rhBMP-2/CPM 2.0 mg/mL		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	14		
Units: Participants				
Ease of Preparing-satisfactory	15	14		
Ease of Preparing-unsatisfactory	0	0		
Ease of Injecting-satisfactory	15	11		
Ease of Injecting-unsatisfactory	0	3		
Ability to inject entire volume-satisfactory	13	12		
Ability to inject entire volume-unsatisfactory	2	2		
Localization within Proximal Femur-satisfactory	15	11		
Localization within Proximal Femur-unsatisfactory	0	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage Change from Baseline in Serum Biomarkers of Bone Turnover

End point title	Percentage Change from Baseline in Serum Biomarkers of Bone Turnover

End point description:

Biomarkers of bone formation and resorption and serum biomarkers of bone turnover with percentage change from baseline are listed by participant. No significant changes in biochemical markers of bone turnover were identified. Additionally, the number of partcipants treated was too small to draw any further conclusions.

End point type	Secondary

End point timeframe:

12 months

End point values	Standard of Care Control	rhBMP-2/CPM 1.0 mg/mL	rhBMP-2/CPM 2.0 mg/mL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	0[5]	0[6]	0[7]	
Units: percentage of participants				

Notes:

[5] - The number of participants treated was too small to draw any conclusion.

[6] - The number of participants treated was too small to draw any conclusion.

[7] - The number of participants treated was too small to draw any conclusion.

Statistical analyses

No statistical analyses for this end point

Secondary: Timecourse Distribution of Areal Bone Mineral Density (BMD) for the contralateral: Region of Interest: for Total Hip

End point title	Timecourse Distribution of Areal Bone Mineral Density (BMD) for the contralateral: Region of Interest: for Total Hip

End point description:

Evaluating local changes (expected increases) in BMD after administration of rhBMP-2/CPM, compared to those observed with systemic osteoporosis therapy alone. The percentage change from baseline in BMD for total hip (assessed by DXA) is presented for the contralateral (untreated) hip below.

End point type	Secondary

End point timeframe:

36 months

End point values	Standard of Care Control	rhBMP-2/CPM 1.0 mg/mL	rhBMP-2/CPM 2.0 mg/mL	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	10	12	12	
Units: mg/cm2				
arithmetic mean (standard deviation)	0.73 (± 0.057)	0.71 (± 0.045)	0.71 (± 0.11)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected from the time of written informed consent through 3 years, month 36 (Visit 10) for SOC participants and through 5 years, month 60 for participants who either received 1.0 mg/mL or 2.0 mg/mL of rhBMP-2/CPM.

Adverse event reporting additional description:

The as-treated population included randomly assigned participants who received at least 1 dose of rhBMP-2/CPM or comparator agent. Participants in the as-treated population are grouped according to the treatment they received (not the treatment to which they were randomly assigned).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Standard of Care Control

Reporting group description:

Participants had received systemic osteoporosis therapy with an oral bisphosphonate plus supplemental calcium, and vitamin D as prescribed by the study physician.

Reporting group title	rhBMP-2/CPm 2.0 mg/mL

Reporting group description:

Participants had received 2 mg/mL rhBMP 2/CPM administered via intraosseous injection administered percutaneously to the proximal femur. Participants in treatment groups additionally received SOC treatment for OP.

Reporting group title	rhBMP-2/CPM 1.0 mg/mL

Reporting group description:

Participants had received 1 mg/mL rhBMP 2/CPM administered via intraosseous injection administered percutaneously to the proximal femur. Participants in treatment groups additionally received SOC treatment for OP.

Serious adverse events	Standard of Care Control	rhBMP-2/CPm 2.0 mg/mL	rhBMP-2/CPM 1.0 mg/mL
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 17 (17.65%)	7 / 14 (50.00%)	7 / 15 (46.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Investigations			
Nuclear magnetic resonance imaging abnormal			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			

subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thyroid neoplasm			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Humerus fracture			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Procedural pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Rib fracture			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Road traffic accident			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Fall			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Femoral neck fracture			

subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Angina Pectoris			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Myocardial Infarction			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Intracranial aneurysm			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Syncope			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Transient ischaemic attack			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Oesophagitis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pneumothorax			

subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary mass			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Bone infarction			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Intervertebral disc protrusion			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Joint range of motion decreased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteoarthritis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Osteonecrosis			
subjects affected / exposed	0 / 17 (0.00%)	2 / 14 (14.29%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	2 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchopneumonia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Standard of Care Control	rhBMP-2/CPm 2.0 mg/mL	rhBMP-2/CPM 1.0 mg/mL
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 17 (76.47%)	12 / 14 (85.71%)	15 / 15 (100.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Benign neoplasm of skin			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Choroid melanoma			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Colon adenoma			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Dysplastic naevus			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1

Neoplasm			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Seborrhoeic keratosis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Skin papilloma			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Tumour ulceration			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Aortic calcification			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Hypertension			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Hypotension			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Vascular calcification			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Breakthrough pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Chills			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Facial pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Fatigue			

subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Gait deviation			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Gait disturbance			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Injection site bruising			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Injection site discharge			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Injection site erythema			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Injection site mass			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Injection site pain			
subjects affected / exposed	0 / 17 (0.00%)	5 / 14 (35.71%)	0 / 15 (0.00%)
occurrences (all)	0	8	0
Injection site swelling			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Malaise			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Oedema			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Non-cardiac chest pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral			

subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Pain			
subjects affected / exposed	2 / 17 (11.76%)	1 / 14 (7.14%)	2 / 15 (13.33%)
occurrences (all)	2	1	3
Peripheral swelling			
subjects affected / exposed	1 / 17 (5.88%)	1 / 14 (7.14%)	1 / 15 (6.67%)
occurrences (all)	1	1	2
Pyrexia			
subjects affected / exposed	0 / 17 (0.00%)	2 / 14 (14.29%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Soft tissue inflammation			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Reproductive system and breast disorders			
Vulvovaginal discomfort			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Vulvovaginal pruritus			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Atelectasis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	2 / 15 (13.33%)
occurrences (all)	0	1	2
Choking sensation			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Cough			
subjects affected / exposed	3 / 17 (17.65%)	3 / 14 (21.43%)	1 / 15 (6.67%)
occurrences (all)	3	3	1
Dyspnoea exertional			

subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Nasal congestion			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Oropharyngeal pain			
subjects affected / exposed	2 / 17 (11.76%)	1 / 14 (7.14%)	2 / 15 (13.33%)
occurrences (all)	2	1	2
Productive cough			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Rhinorrhoea			
subjects affected / exposed	1 / 17 (5.88%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Sinus congestion			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Anxiety			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Insomnia			
subjects affected / exposed	0 / 17 (0.00%)	2 / 14 (14.29%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Chest X-ray abnormal			

subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Scan bone marrow abnormal			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Urine output increased			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Weight decreased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Clavicle fracture			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Contusion			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	1 / 15 (6.67%)
occurrences (all)	0	2	1
Epicondylitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Fall			
subjects affected / exposed	4 / 17 (23.53%)	3 / 14 (21.43%)	5 / 15 (33.33%)
occurrences (all)	5	6	5
Fibula fracture			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Hand fracture			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Head injury			

subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Humerus fracture			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Injection related reaction			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Joint injury			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Laceration			
subjects affected / exposed	1 / 17 (5.88%)	1 / 14 (7.14%)	1 / 15 (6.67%)
occurrences (all)	1	1	1
Ligament sprain			
subjects affected / exposed	2 / 17 (11.76%)	0 / 14 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Limb injury			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Lower limb fracture			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Muscle strain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Patella fracture			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Procedural hypotension			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Procedural pain			
subjects affected / exposed	0 / 17 (0.00%)	5 / 14 (35.71%)	2 / 15 (13.33%)
occurrences (all)	0	6	3
Road traffic accident			

subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Skeletal injury			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	4	0
Skin abrasion			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Superficial injury of eye			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Thermal burn			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Wound			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Wrist fracture			
subjects affected / exposed	0 / 17 (0.00%)	2 / 14 (14.29%)	0 / 15 (0.00%)
occurrences (all)	0	3	0
Cardiac disorders			
Atrioventricular block first degree			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Chronotropic incompetence			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Supraventricular extrasystoles			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Nervous system disorders			
Balance disorder			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Dizziness			

subjects affected / exposed	1 / 17 (5.88%)	2 / 14 (14.29%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Dizziness postural			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Headache			
subjects affected / exposed	1 / 17 (5.88%)	2 / 14 (14.29%)	1 / 15 (6.67%)
occurrences (all)	1	3	4
Hypoaesthesia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	4	0
Lethargy			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Loss of consciousness			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Meralgia paraesthetica			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Neuralgia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Peroneal nerve palsy			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Sciatica			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Sinus headache			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	11
VIIth nerve paralysis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Blood and lymphatic system disorders			

Anaemia			
subjects affected / exposed	1 / 17 (5.88%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Bone marrow oedema			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Lymph node calcification			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Lymphadenopathy			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Vertigo			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Eye disorders			
Blepharitis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Choroidal haemorrhage			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Dark circles under eyes			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Eye pain			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Eyelid ptosis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Cataract			

subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Macular generation			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Ocular hyperaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Retinal haemorrhage			
subjects affected / exposed	1 / 17 (5.88%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Visual acuity reduced			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Abdominal pain upper			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Cheilitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	3 / 15 (20.00%)
occurrences (all)	1	0	3
Diarrhoea			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Dry mouth			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Dyspepsia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	0 / 15 (0.00%)
occurrences (all)	3	0	0

Dysphagia			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Gastric ulcer			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Gastritis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Haemorrhoids			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Hiatus hernia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Nausea			
subjects affected / exposed	1 / 17 (5.88%)	5 / 14 (35.71%)	6 / 15 (40.00%)
occurrences (all)	2	8	6
Oesophagitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Oral discomfort			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Pancreatic cyst			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Vomiting			
subjects affected / exposed	0 / 17 (0.00%)	3 / 14 (21.43%)	3 / 15 (20.00%)
occurrences (all)	0	4	4
Skin and subcutaneous tissue disorders			
Acne			

subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Dandruff			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Dermatitis allergic			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Dry skin			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Erythema			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	2 / 15 (13.33%)
occurrences (all)	0	1	2
Ingrowing nail			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Rash			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Skin lesion			
subjects affected / exposed	1 / 17 (5.88%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	1	1	0
Urticaria			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Haematuria			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Incontinence			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1

Renal failure			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Endocrine disorders			
Hypothyroidism			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	5 / 17 (29.41%)	9 / 14 (64.29%)	12 / 15 (80.00%)
occurrences (all)	9	19	24
Arthritis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	0 / 15 (0.00%)
occurrences (all)	2	0	0
Back pain			
subjects affected / exposed	2 / 17 (11.76%)	3 / 14 (21.43%)	4 / 15 (26.67%)
occurrences (all)	5	3	23
Bone pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Bursitis			
subjects affected / exposed	1 / 17 (5.88%)	1 / 14 (7.14%)	2 / 15 (13.33%)
occurrences (all)	1	2	2
Exostosis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Foot deformity			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Groin pain			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	2 / 15 (13.33%)
occurrences (all)	0	0	2
Intervertebral disc degeneration			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	1
Joint effusion			

subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Joint range of motion decreased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Joint swelling			
subjects affected / exposed	2 / 17 (11.76%)	4 / 14 (28.57%)	3 / 15 (20.00%)
occurrences (all)	2	7	4
Mobility decreased			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Limb discomfort			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Muscle spasms			
subjects affected / exposed	1 / 17 (5.88%)	1 / 14 (7.14%)	2 / 15 (13.33%)
occurrences (all)	1	4	3
Muscle swelling			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Muscular weakness			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Musculoskeletal pain			
subjects affected / exposed	2 / 17 (11.76%)	2 / 14 (14.29%)	3 / 15 (20.00%)
occurrences (all)	2	2	9
Musculoskeletal discomfort			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Musculoskeletal stiffness			
subjects affected / exposed	2 / 17 (11.76%)	2 / 14 (14.29%)	1 / 15 (6.67%)
occurrences (all)	2	3	1
Myalgia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	2 / 15 (13.33%)
occurrences (all)	1	0	3
Osteitis			

subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Osteoarthritis			
subjects affected / exposed	1 / 17 (5.88%)	2 / 14 (14.29%)	2 / 15 (13.33%)
occurrences (all)	1	3	2
Pain in extremity			
subjects affected / exposed	3 / 17 (17.65%)	4 / 14 (28.57%)	2 / 15 (13.33%)
occurrences (all)	3	11	2
Pain in jaw			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Periarthritis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Plantar fasciitis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	1	0	2
Scoliosis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Spinal osteoarthritis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Synovitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	2
Temporomandibular joint syndrome			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Tendonitis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Vertebral osteophyte			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Weight bearing difficulty			

subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	2 / 15 (13.33%)
occurrences (all)	0	1	2
Infections and infestations			
Arthritis infective			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Bronchitis			
subjects affected / exposed	1 / 17 (5.88%)	2 / 14 (14.29%)	2 / 15 (13.33%)
occurrences (all)	3	2	2
Coccidioidomycosis			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Cystitis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	4	0
Diarrhoea infectious			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Gastroenteritis viral			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Influenza			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Labyrinthitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	3
Lung infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
subjects affected / exposed	0 / 17 (0.00%)	2 / 14 (14.29%)	0 / 15 (0.00%)
occurrences (all)	0	4	0
Onychomycosis			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0

Oral herpes			
subjects affected / exposed	0 / 17 (0.00%)	2 / 14 (14.29%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Osteomyelitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Pharyngitis streptococcal			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Pneumonia			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	1 / 15 (6.67%)
occurrences (all)	0	1	1
Rhinitis			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Sinusitis			
subjects affected / exposed	1 / 17 (5.88%)	1 / 14 (7.14%)	2 / 15 (13.33%)
occurrences (all)	2	1	2
Tooth infection			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 17 (0.00%)	2 / 14 (14.29%)	0 / 15 (0.00%)
occurrences (all)	0	2	0
Urinary tract infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Hypercholesterolaemia			

subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0
Hypokalaemia			
subjects affected / exposed	1 / 17 (5.88%)	0 / 14 (0.00%)	0 / 15 (0.00%)
occurrences (all)	1	0	0
Iodine deficiency			
subjects affected / exposed	0 / 17 (0.00%)	0 / 14 (0.00%)	1 / 15 (6.67%)
occurrences (all)	0	0	1
Type 2 diabetes mellitus			
subjects affected / exposed	0 / 17 (0.00%)	1 / 14 (7.14%)	0 / 15 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 October 2009	In Protocol amendment 1, the following changes were made; reduced number and type of diagnostic tests for Cohort 2, Removed mandatory postdosing hospital stay for Cohort 2, Extended VAS assessment, Revised Risk/Benefits Section, Shifted full physical examination from screening to predosing and added parameters for obtaining detailed medical history, Incorporated predefined stopping criteria specific to Cohort 2, Incorporated upper age limit of 85 years old. [Previously, participants ≥65 years were allowed to be enrolled], Revised terminology to describe SOC, Revised permitted/prohibited concomitant therapies, Expanded window between randomization and treatment from 24 hours to 1 week (7 days), Clarified eligibility criterion regarding use of anticonvulsant agents, Physically revised protocol so that sections of Synopsis and Body matched, Provided criteria for participant discharge, Added guidelines for pain management, Revised contact information to reflect changes in Wyeth study staff, Clarified dosing regimens and provide guidelines for calcium and vitamin D Revised verbiage for clarity and to better reflect original protocol intent.
29 September 2010	In protocol amendment 2, bone resorption to key safety events was added.
19 September 2011	In Protocol amendment 3, the following changes were made; MRI test was added as a mandatory procedure at the 24 month visit for Cohort 2 participants. MRI was a mandatory study procedure at the 36 month visit for all participants Volumetric QCT was not needed for safety follow-up; and therefore, was replaced with the MRI test. Cohort 1 received vQCT at the 24 month visit; Cohort 2 did not receive vQCT at 24 months, Radiation exposure was the same for Cohort 1 participants, but not for Cohort 2 participants because participants in this group did not receive vQCT at 24 months, Clarified the difference between follow-up vQCT scans for Cohort 1 and Cohort 2.
01 March 2012	In Protocol amendment 4, the following changes were made; text updated to reflect that Emergency contact, as well as SAE reporting fax, is no longer centralized in the USA. Each country has its own emergency contact phone number and SAE fax reporting number, Medication errors text moved and AE reporting text updated to comply with Pfizer language and format, Study suspension, termination and completion text removed; redundant with Section 5 Synopsis Ethical Considerations, and text added with respect to reporting of safety issues and serious breaches of the protocol or ICH GCP.

26 October 2012	In Protocol amendment 5, the following changes were made; projected duration of the study was updated from 46 months to 70 months. Taking into consideration the 2 confirmed cases of ON, which was considered as an important identified risk in participants with OP who received a percutaneous injection of rhBMP 2/CPM administered intraosseously into the proximal femur, Pfizer decided it would be necessary to continue following participants in the 1 and 2 mg/mL rhBMP 2/CPM treatment arms for a total of 5 years after TA injection, Duration of participant participation was updated from 36 months to 60 months for participants who received the TA (see above), In the follow-up period, additional annual evaluations at 48 and 60 months for participants who received (either 1 mg/mL or 2 mg/mL of rhBMP 2/CPM were added. This long-term extension was intended to provide supportive safety data for inclusion in the regulatory filing. Participants were to be followed for AEs and SAEs during this time, The protocol flowchart was updated to reflect the 2 additional safety evaluations scheduled at 48 and 60 month post TA injection for participants in the 1 and 2 mg/mL rhBMP 2/CPM treatment arms. SOC participants were planned to complete the study following the 36 month follow up visit. Because participants were to be followed for safety reasons after 36 months, text was amended to state that the investigator could decide whether or not the supplemental calcium and vitamin D as well as BP therapy was needed for each participant, Evaluations at additional follow-up visits added to the protocol text and Imaging modality section was updated in order to add Pelvic MRI as imaging procedure, and also to document there was no radiation exposure with pelvic MRI procedure.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
26 August 2010	Enrollment was terminated on 26 August 2010, due to the finding of an unexpected proximal femur fracture in a study medication-injected participant shortly after study medication injection and long-term follow-up of participants in the rhBMP-2/CPM-administered groups was extended from 36 months to 60 months.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Due to early termination of participant enrollment, mainly descriptive statistics were provided, and no statistical tests were performed. The study was terminated early due to safety concerns.

Notes: