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GENERIC DRUG NAME and/or COMPOUND NUMBER: rhBMP-2/CPM

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: This drug is not marketed in the United States

NATIONAL CLINICAL TRIAL NO.: NCT00384358

PROTOCOL NO.: B1921004 (3100N7-211-WW)

PROTOCOL TITLE: FINAL REPORT: A PHASE 2, MULTICENTER, SINGLE-BLIND, RANDOMIZED, STRATIFIED, STANDARD-OF-CARE CONTROLLED, FEASIBILITY AND SAFETY STUDY OF RHBMP-2/CPM AS AN ADJUVANT THERAPY FOR FRACTURES OF THE PROXIMAL FEMUR

Study Center(s): This was a multicenter trial conducted in 23 investigational sites: 7 in the United States, 3 in Canada, 4 in Australia, 2 each in France, Finland, Hungary, and the United Kingdom and 1 in Sweden.

Study Initiation and Completion Dates: 1 December 2006 to 22 June 2010

Phase of Development: Phase 2

Study Objective(s): The primary objective of the study was to demonstrate the safety of administering recombinant human bone morphogenetic protein-2/calcium phosphate matrix (rhBMP-2/CPM) (either 1.0 mg/mL or 2.0 mg/mL) as an adjunct to internal fixation in subjects with fractures of the proximal femur. Using a noninferiority approach, the key safety outcome was the incidence of secondary fracture displacement among subjects treated with rhBMP-2/CPM and those receiving standard surgical treatment (internal fixation) alone. Supportive safety variables included the occurrence of adverse events (AEs), physical examination of the limb under study, radiographic assessments, laboratory measurements, and subjects' self-report of pain in the region under study (RUS) using a 50-mm visual analogue scale (VAS).

The secondary objectives of the study were to:

1. Establish a satisfactory method of administering rhBMP-2/CPM to implement in a phase 3 efficacy trial in this clinical indication.

2. Estimate the success and failure rates associated with the following key fracture outcomes, for consideration in sample size projections for a phase 3 clinical efficacy trial:

- Fracture healing (clinical and radiographic), without evidence of secondary fracture displacement.

- Health outcomes (functional status and satisfaction with treatment outcome), using the Short Musculoskeletal Function Assessment (SMFA) instrument (subject self report).

- Functional mobility, using the timed up and go (TUG) test.

METHODS

Study Design: This was a phase 2, multicenter, single-blind, randomized, parallel dose study to demonstrate the safety of administering 2 concentrations of rhBMP-2/CPM (either 1.0 mg/mL or 2.0 mg/mL) as an adjuvant therapy for proximal femur fractures treated with internal fixation. The study population was comprised of subjects with either femoral neck or intertrochanteric fractures. The treatment assignments were stratified by fracture type as fracture outcome was expected to differ between femoral neck and intertrochanteric fractures. Within each stratum, randomization of treatment assignments was performed in a 1:1:1 ratio, with subjects assigned to 1 of the 3 following treatment groups:

- 1.0 mg/mL rhBMP-2/CPM + standard of care (SOC)

- 2.0 mg/mL rhBMP-2/CPM + SOC

- SOC alone

All subjects in the trial received SOC (ie, fracture reduction and internal fixation by means of multiple parallel interfragmentary screws, sliding hip screws or cephalomedullary nail) and subjects assigned to either one of the active treatment arms received rhBMP-2/CPM as an adjunct to SOC. The duration of the entire study was approximately 38 months.

Screening evaluations were performed during the interval between injury and fracture reduction. Follow-up assessments to support the primary objective occurred at 2, 6, 12, 16, 20, and 26 weeks after administration of the randomized treatment assignment. Long-term safety follow-up assessments were performed at 1 year and 2 years after treatment.

Number of Subjects (Planned and Analyzed): The number of subjects planned for this study was 108, grouped as 36 subjects in each treatment (SOC group, 1.0 mg/mL rhBMP-2/CPM treatment group, and 2.0 mg/mL rhBMP-2/CPM treatment group). A total of 115 subjects were randomly assigned; 38 subjects to the SOC group, 39 subjects to the 1.0 mg/mL rhBMP-2/CPM treatment group, and 38 subjects to the 2.0 mg/mL rhBMP-2/CPM treatment group, including 7 subjects who discontinued before receiving the assigned treatment. A total of 108 subjects were treated.

Diagnosis and Main Criteria for Inclusion: Adult subjects (aged ≥55 years) with acute closed fracture of the proximal femur; displaced femoral neck fracture (Garden Type III or IV); basilar neck fracture (Orthopaedic Trauma Association [OTA] Classification 31-B2); or

unstable intertrochanteric femur fracture (OTA Classification 31-A2 or 31-A3) to be treated with anatomic reduction and internal fixation within 48 hours following injury.

Study Treatment: The test article in this study consisted of 1.0 mg/mL of rhBMP-2/CPM or 2.0 mg/mL of rhBMP-2/CPM. The test article was administered by trained and qualified orthopedic surgeons in the operating theatre under fluoroscopic guidance at the time of fracture reduction and fixation while subjects were anesthetized. The injection occurred within 15 minutes of the preparation of the test article. Each kit provided up to 3 mL of test article. The total volume of test article required to treat subjects with femoral neck fractures was 3 (± 0.5) mL; therefore, only 1 kit was assigned. However, subjects with intertrochanteric fractures received up to 2 kits per subject because a larger volume, 5 (± 1.0) mL, of material was required to be delivered to the fracture site. Depending on the fixation construct used, the test article was either administered intraosseously (eg, interfragmentary screws or screw and side plate fixation) once provisional fixation of the fracture was achieved but before final application of the entire fixation construct occurred, or periosseously (eg, cephalomedullary nail).

Efficacy Evaluations: The efficacy variables in this study were outcomes of fracture union and restoration of functional mobility. The presence of radiographic fracture union was assessed on the basis of findings from plain radiographs and/or computed tomography (CT) scans acquired during the study by an independent, blinded, Central Evaluations Committee (CEC), a panel composed of independent physicians, each with clinical expertise in orthopedic surgery or musculoskeletal radiology and none of whom were directly involved in the treatment of subjects enrolled in the trial. Radiographic fracture union required visualization of either bridging trabecular bone across the fracture site and/or obliteration (disappearance) of the fracture line(s) on 2 out of 4 diaphyseal aspects on each of 2 orthogonal radiographic views. Restoration of functional mobility was assessed based upon absence of pain at the fracture site with full weight bearing.

Immunogenicity Evaluations: As part of the safety evaluation, serum samples were collected at baseline and at visits scheduled for 6 weeks, 20 weeks, and 1 year to assess the prevalence and incidence of anti-BMP-2 antibody formation using a validated enzyme-linked immunosorbent assay (ELISA).

Safety Evaluations: The key safety outcome was the incidence of secondary fracture displacement among subjects treated with rhBMP-2/CPM and those receiving standard surgical treatment (internal fixation) alone. Radiographic evidence of secondary fracture displacement was assessed by the CEC according to pre-established criteria that indicated a clinically significant loss of fracture reduction (varus deformity >10 degrees, screw extrusion >20 mm, cut-out into the femoral head, 5 degree change in angle of parallel fixation screws and breakage, bending disassembly or pull-off of any component of the fracture fixation construct). Consensus was required by the CEC to determine the study time point at which secondary fracture displacement occurred. If consensus was not achieved for an individual subject, an adjudicated reading was performed to determine secondary fracture displacement, and the adjudicated reading was used as the final, definitive assessment for that time point.

Other safety assessments included: monitoring of AEs, antibody formation to BMP-2, hematology and chemistry laboratory testing, findings from physical and radiographic examinations, subjective reports of pain, and functional outcome assessments.

Other assessment methods: The feasibility of rhBMP-2/CPM administration was evaluated using an investigator questionnaire and a radiographic comparison to verify whether the test article migrated from the site of administration.

Statistical Methods: The primary safety analysis of secondary fracture displacement was based on the evaluable population and all other additional statistical analyses were based on the intent-to-treat (ITT) population. Evaluable subjects received the assigned randomized treatment, had appropriate placement of the test article (if randomized to an active treatment), and their fractures were adequately reduced and fixed based on the CEC assessment. The primary analysis was the noninferiority of the rate of fractures without secondary displacement at 6 months. This analysis was based on the 95% confidence interval (CI) of the difference in proportions based on the standard error calculation assuming $p1 \neq p2$. On the basis of established guidelines for clinical effectiveness endpoints for anti-infective drugs with success rates ranging from 70% to 79% if the lower CI is greater than –20%, noninferiority was to be assumed. An evaluable subject has received the randomized treatment assignment and correct amount and placement of test article (if applicable), has anatomic fracture reduction and fracture fixation and has a verifiable fracture outcome.

RESULTS

Subject Disposition and Demography: Of the 117 subjects that were screened for participation in the study, 115 were randomly assigned; 38 subjects to the SOC group, 39 subjects to the 1.0 mg/mL rhBMP-2/CPM treatment group, and 38 subjects to the 2.0 mg/mL rhBMP-2/CPM treatment group, including 7 subjects who discontinued before receiving the assigned treatment. A total of 108 subjects were treated and included in the safety analysis. The efficacy analysis was performed on 85 subjects in the evaluable population and 108 subjects in the ITT population. Sixty-eight (68, 59%) subjects completed the study and a total of 47 (41%) subjects were withdrawn from the study. Subject disposition is presented in Table 1.

Table 1 . Summary of Subject Disposition

	Treatment			
	Standard of Care Control	**1.0 mg/mL rhBMP-2/CPM Acute**	**2.0 mg/mL rhBMP-2/CPM Acute**	**Total**
Screened				117
Randomized	38	39	38	115
Discontinued Subjects	0	4 (10)	3 (8)	7 (6)
Treated	38 (100)	35 (90)	35 (92)	108 (94)
Early Conclusion	13 (34)	15 (38)	19 (50)	47 (41)
Adverse Event	1 (3)	1 (3)	0	2 (2)
Subject Request	6 (16)	2 (5)	6 (16)	14 (12)
Investigator Request	0	4 (10)	0	4 (3)
Death	3 (8)	6 (15)	6 (16)	15 (13)
Protocol Violation	1 (3)	0	0	1 (<1)
Lost to Follow-up	1 (3)	1 (3)	4 (11)	6 (5)
Other	1 (3)	1 (3)	3 (8)	5 (4)
Completed Study	25 (66)	24 (62)	19 (50)	68 (59)

Abbreviations: CPM=calcium phosphate matrix; rhBMP-2=recombinant human bone morphogenetic protein-2.

The study population consisted of 75 (69%) female and 33 (31%) male subjects aged 55 to 92 years, with a mean age of 75.7 years. Minor differences in baseline demographics among treatment groups were noted, but were not deemed to have affected the safety outcomes. A summary of the subject demography is presented in Table 2.

Table 2. Summary of Demographic Characteristics

	Treatment			
Characteristic	**Standard of Care Control (n = 38)**	**1.0 mg/mL rhBMP-2/CPM Acute (n = 35)**	**2.0 mg/mL rhBMP-2/CPM Acute (n = 35)**	**Total (n = 108)**
Age (yr)				
N	38	35	35	108
Mean	74.29	75.46	77.49	75.70
Standard Deviation	8.49	9.62	10.51	9.55
Minimum	55.00	57.00	55.00	55.00
Maximum	88.00	92.00	91.00	92.00
Median	74.00	76.00	80.00	77.00
Age Category				
< 65	7 (18)	7 (20)	6 (17)	20 (19)
≥ 65	31 (82)	28 (80)	29 (83)	88 (81)
Sex, N (%)				
Female	25 (66)	24 (69)	26 (74)	75 (69)
Male	13 (34)	11 (31)	9 (26)	33 (31)
Race, N (%)				
White	38 (100)	34 (97)	33 (94)	105 (97)
Black	0	1 (3)	0	1 (1)
Other	0	0	2 (6)	2 (2)
Height (cm)				
N	36	34	35	105
Mean	166.11	166.54	162.79	165.15
Standard Deviation	8.61	10.04	8.02	8.99
Minimum	150.00	150.00	148.00	148.00
Maximum	188.00	188.00	178.00	188.00
Median	165.10	165.05	165.00	165.00
Missing	2	1	0	3
Weight (kg)				
N	36	34	35	105
Mean	68.88	70.32	66.06	68.41
Standard Deviation	16.20	19.14	15.40	16.89
Minimum	42.60	40.00	43.50	40.00
Maximum	100.00	135.00	105.00	135.00
Median	64.95	66.50	64.00	65.00
Missing	2	1	0	3
Tobacco Use, N (%)				
No	34 (89)	32 (91)	34 (97)	100 (93)
Yes	4 (11)	3 (9)	1 (3)	8 (7)

Abbreviations: CPM=calcium phosphate matrix; rhBMP-2=recombinant human bone morphogenetic protein-2.

Efficacy Results: For the ITT population at the time of final analysis, a slightly higher percentage of subjects in the 1.0 mg/mL rhBMP-2/CPM (94.1%) treatment group achieved radiographic fracture union than the 2.0 mg/mL rhBMP-2/CPM (90.6%) treatment group and the SOC group (88.9%), but this was not deemed significant. Median time to fracture union was similar in the SOC group, 1.0 mg/mL rhBMP-2/CPM treatment group and the 2.0 mg/mL rhBMP-2/CPM treatment group (15.6, 15.9, and 15.9 weeks, respectively).

rhBMP-2/CPM did not reduce the time to fracture union in subjects with displaced femoral neck or intertrochanteric fractures and it's clinical development has been halted.

Immunogenicity Results: Overall, an authentic immune response developed in 1 (3%) subject each in the SOC group and 1.0 mg/mL rhBMP-2/CPM treatment group, and 2 (6%) subjects in the 2.0 mg/mL rhBMP-2/CPM treatment group. No neutralizing anti-BMP-2 antibodies were found in the subjects presenting with elevated anti-BMP-2 antibodies.

Safety Results: The analysis of the rate of secondary fracture displacement was performed on the evaluable population and results are presented in Table 3. Noninferiority in the incidence of secondary fracture displacement was assumed if the lower confidence limit of the 95% CI was greater than -20%. Noninferiority was assumed for the 2.0 mg/mL rhBMP-2/CPM treatment group when the difference in proportions 95% CI was pooled (−19.4, 23.1) but not when the difference in proportions 95% CI was adjusted for femoral neck/interchanteric strata (−20.6, 23.9). For the 1.0 mg/mL rhBMP-2/CPM treatment group, noninferiority was assumed when the difference in proportions 95% CI was adjusted for femoral neck/interchanteric strata (-18.7, 18.9), but not when the difference in proportions 95% CI was pooled (-24.6, 18.4).

Table 3. Primary Non Inferiority Analysis of the Secondary Displacement Fracture Rate at 6 months: Evaluable Population

	Treatment		
	Standard of Care Control (n = 32)	**1.0 mg/mL rhBMP-2/CPM Acute (n = 28)**	**2.0 mg/mL rhBMP-2/CPM Acute (n = 25)**
Subjects Without Secondary Displacement (n, %)	25(78.1)	21(75.0)	20(80.0)
Femoral Neck	7(58.3)	5(45.5)	8(72.7)
Intertrochanteric	18(90.0)	16(94.1)	12(85.7)
% Difference in Proportions (Pooled) [a]		−3.1	1.9
% Difference in Proportions 95% CI (Pooled) [a]		−24.6,18.4	−19.4,23.1
% Difference in Proportions (Minimum Risk) [b]		0.1	1.6
% Difference in Proportions 95% CI (Minimum Risk) [b]		−18.7,18.9	−20.6,23.9
Strata by Treatment Group Interaction P-Value [c]		0.3917	

Abbreviations: CPM=calcium phosphate matrix; CI=confidence interval; rhBMP-2=recombinant human bone morphogenetic protein-2.

a. Not adjusted for femoral neck/intertrochanteric strata.
b. Adjusted for femoral neck/interchanteric strata.
c. Logistic model: secondary displacement ~ fracture strata + treatment group + strata*treatment interaction.

The observed data does not show an increase in the rate of secondary fracture displacement. However, since the analyses just missed the statistical criterion of noninferiority, it cannot be concluded that rhBMP-2/CPM does not increase the rate of secondary fracture displacement

in subjects with displaced femoral neck or intertrochanteric fractures and its clinical development has been stopped. Many subjects had a lack of adequate fracture reduction or insufficient fracture fixation. This has led to many primary fracture displacements, limiting to 78.7% of the population evaluated for the primary safety endpoint. The frequent primary fracture displacement may have been triggered by the protocol requiring a conservative treatment to treat unstable fractures of the proximal femur. Intervention with rhBMP-2/CPM did not appear to have protected subjects against primary displacement or secondary fracture displacement. Current SOC, using arthroplasty to treat displaced, unstable fractures seems therefore more appropriate.

A total of 107 (99%) subjects had at least 1 treatment-emergent adverse event (TEAE): 37 (97%) subjects in the SOC group, 35 (100%) subjects in the 1.0 mg/mL rhBMP-2/CPM treatment group, and 35 (100%) subjects in the 2.0 mg/mL rhBMP-2/CPM treatment group. The most common TEAEs were carbon dioxide decreased (41%), haemoglobin decreased (40%), blood glucose increased (38%), blood calcium decreased (37%), haematocrit decreased (36%), hyperglycaemia (31%), anaemia (26%), and constipation (23%). There were no significant differences among treatment groups for these TEAEs as well as protocol define key safety events. No potential safety signal was identified. No significant differences among treatment groups could be identified, when investigator related TEAEs were considered. The TEAEs reported by more than 10% of the subjects are presented in Table 4.

Table 4. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events in More than 10% of the Subjects

	Treatment			
System Organ Class [a] Preferred Term	**Standard of Care Control n=38**	**1.0 mg/mL rhBMP-2/CPM Acute n=35**	**2.0 mg/mL rhBMP-2/CPM Acute n=35**	**Total n=108**
Any Adverse Event	37 (97)	35 (100)	35 (100)	107 (99)
Blood and lymphatic system disorders	14 (37)	9 (26)	8 (23)	31 (29)
Anaemia	13 (34)	8 (23)	7 (20)	28 (26)
Cardiac disorders	12 (32)	11 (31)	5 (14)	28 (26)
Tachycardia	4 (11)	2 (6)	1 (3)	7 (6)
Gastrointestinal disorders	17 (45)	12 (34)	13 (37)	42 (39)
Constipation	9 (24)	8 (23)	8 (23)	25 (23)
Diarrhoea	3 (8)	1 (3)	4 (11)	8 (7)
Nausea	7 (18)	4 (11)	9 (26)	20 (19)
General disorders and administration site conditions	17 (45)	15 (43)	13 (37)	45 (42)
Oedema peripheral	8 (21)	4 (11)	4 (11)	16 (15)
Pyrexia	5 (13)	3 (9)	2 (6)	10 (9)
Swelling	1 (3)	2 (6)	5 (14)	8 (7)
Infections and infestations	17 (45)	11 (31)	12 (34)	40 (37)
Urinary tract infection	5 (13)	5 (14)	5 (14)	15 (14)
Injury, poisoning and procedural complications	21 (55)	13 (37)	16 (46)	50 (46)
Contusion	5 (13)	2 (6)	2 (6)	9 (8)
Postoperative heterotopic calcification	7 (18)	4 (11)	9 (26)	20 (19)
Procedural pain	6 (16)	2 (6)	2 (6)	10 (9)
Investigations	33 (87)	34 (97)	33 (94)	100 (93)

Table 4. Number (%) of Subjects Reporting Treatment-Emergent Adverse Events in More than 10% of the Subjects

System Organ Class [a] Preferred Term	Treatment: Standard of Care Control n=38	1.0 mg/mL rhBMP-2/CPM Acute n=35	2.0 mg/mL rhBMP-2/CPM Acute n=35	Total n=108
Alanine aminotransferase increased	1 (3)	3 (9)	4 (11)	8 (7)
Aspartate aminotransferase increased	1 (3)	4 (11)	3 (9)	8 (7)
Blood alkaline phosphatase increased	4 (11)	9 (26)	9 (26)	22 (20)
Blood calcium decreased	14 (37)	14 (40)	12 (34)	40 (37)
Blood creatinine increased	5 (13)	1 (3)	2 (6)	8 (7)
Blood glucose increased	13 (34)	16 (46)	12 (34)	41 (38)
Blood lactate dehydrogenase increased	4 (11)	2 (6)	3 (9)	9 (8)
Blood phosphorus decreased	6 (16)	8 (23)	9 (26)	23 (21)
Carbon dioxide decreased	15 (39)	11 (31)	18 (51)	44 (41)
Haematocrit decreased	15 (39)	13 (37)	11 (31)	39 (36)
Haemoglobin decreased	16 (42)	14 (40)	13 (37)	43 (40)
Metabolism and nutrition disorders	18 (47)	15 (43)	17 (49)	50 (46)
Hyperglycaemia	11 (29)	10 (29)	12 (34)	33 (31)
Hypocalcaemia	8 (21)	4 (11)	5 (14)	17 (16)
Hypokalaemia	6 (16)	1 (3)	3 (9)	10 (9)
Hypophosphataemia	8 (21)	1 (3)	3 (9)	12 (11)
Musculoskeletal and connective tissue disorders	19 (50)	18 (51)	15 (43)	52 (48)
Arthralgia	11 (29)	5 (14)	3 (9)	19 (18)
Back pain	5 (13)	4 (11)	0	9 (8)
Bursitis	0	4 (11)	1 (3)	5 (5)
Pain in extremity	4 (11)	2 (6)	4 (11)	10 (9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (8)	1 (3)	4 (11)	8 (7)
Nervous system disorders	10 (26)	11 (31)	8 (23)	29 (27)
Dizziness	2 (5)	5 (14)	0	7 (6)
Psychiatric disorders	8 (21)	7 (20)	5 (14)	20 (19)
Confusional state	4 (11)	3 (9)	2 (6)	9 (8)
Insomnia	4 (11)	3 (9)	2 (6)	9 (8)
Renal and urinary disorders	5 (13)	3 (9)	3 (9)	11 (10)
Respiratory, thoracic and mediastinal disorders	16 (42)	8 (23)	9 (26)	33 (31)
Cough	5 (13)	2 (6)	0	7 (6)
Hypocapnia	7 (18)	4 (11)	5 (14)	16 (15)
Skin and subcutaneous tissue disorders	9 (24)	14 (40)	9 (26)	32 (30)
Erythema	5 (13)	6 (17)	5 (14)	16 (15)
Vascular disorders	12 (32)	8 (23)	4 (11)	24 (22)
Hypotension	4 (11)	4 (11)	2 (6)	10 (9)

Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA)
Abbreviations: CPM=calcium phosphate matrix; rhBMP-2=recombinant human bone morphogenetic protein-2.

a. Totals for the No. of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report two or more different adverse events within the higher level category.

Table 5 summarizes the incidence of treatment-emergent serious adverse events (SAEs) by treatment group and by body system/category of AEs. A total of 58 (54%) subjects reported

SAEs: 23 (61%) subjects in the SOC group, 17 (49%) subjects in the 1.0 mg/mL rhBMP-2/CPM treatment group, and 18 (51%) subjects in the 2.0 mg/mL rhBMP-2/CPM treatment group. No potential treatment effect for either body system class type SAEs or individual SAEs could be identified.

Table 5. Number (%) of Subjects Reporting Treatment-Emergent Serious Adverse Events

	Treatment			
System Organ Class [a] Preferred Term	**Standard of Care Control n=38**	**1.0 mg/mL rhBMP-2/CPM Acute n=35**	**2.0 mg/mL rhBMP-2/CPM Acute n=35**	**Total n=108**
Any Adverse Event	23 (61)	17 (49)	18 (51)	58 (54)
Blood and lymphatic system disorders	1 (3)	1 (3)	2 (6)	4 (4)
Anaemia	0	1 (3)	2 (6)	3 (3)
Coagulopathy	1 (3)	0	0	1 (1)
Haemorrhagic anaemia	1 (3)	0	0	1 (1)
Cardiac disorders	5 (13)	8 (23)	4 (11)	17 (16)
Angina pectoris	0	1 (3)	0	1 (1)
Atrial fibrillation	1 (3)	1 (3)	1 (3)	3 (3)
Cardiac arrest	1 (3)	0	2 (6)	3 (3)
Cardiac failure congestive	0	1 (3)	0	1 (1)
Cardio-respiratory distress	0	1 (3)	0	1 (1)
Cardiopulmonary failure	1 (3)	2 (6)	0	3 (3)
Coronary artery disease	0	1 (3)	0	1 (1)
Myocardial infarction	2 (5)	0	2 (6)	4 (4)
Myocardial ischaemia	0	1 (3)	0	1 (1)
Sinus tachycardia	1 (3)	0	0	1 (1)
Tachycardia	0	0	1 (3)	1 (1)
Gastrointestinal disorders	4 (11)	2 (6)	1 (3)	7 (6)
Colitis	0	1 (3)	0	1 (1)
Gastrointestinal haemorrhage	1 (3)	0	1 (3)	2 (2)
Haematemesis	1 (3)	0	0	1 (1)
Inguinal hernia	1 (3)	0	0	1 (1)
Melaena	1 (3)	0	0	1 (1)
Nausea	1 (3)	1 (3)	0	2 (2)
Vomiting	1 (3)	1 (3)	0	2 (2)
General disorders and administration site conditions	3 (8)	3 (9)	0	6 (6)
Asthenia	1 (3)	0	0	1 (1)
Device dislocation	2 (5)	0	0	2 (2)
Device extrusion	0	1 (3)	0	1 (1)
Device failure	1 (3)	0	0	1 (1)
Oedema	0	1 (3)	0	1 (1)
Oedema peripheral	0	1 (3)	0	1 (1)
Pyrexia	0	1 (3)	0	1 (1)
Hepatobiliary disorders	2 (5)	1 (3)	0	3 (3)
Cholecystitis	0	1 (3)	0	1 (1)
Cholelithiasis	1 (3)	0	0	1 (1)
Hyperbilirubinaemia	1 (3)	0	0	1 (1)
Infections and infestations	8 (21)	3 (9)	2 (6)	13 (12)
Appendicitis	1 (3)	0	0	1 (1)
Appendicitis perforated	1 (3)	0	0	1 (1)

Table 5. Number (%) of Subjects Reporting Treatment-Emergent Serious Adverse Events

System Organ Class [a] Preferred Term	Treatment: Standard of Care Control n=38	Treatment: 1.0 mg/mL rhBMP-2/CPM Acute n=35	Treatment: 2.0 mg/mL rhBMP-2/CPM Acute n=35	Total n=108
Cellulitis	1 (3)	0	1 (3)	2 (2)
Escherichia infection	1 (3)	0	0	1 (1)
Pneumonia	1 (3)	2 (6)	1 (3)	4 (4)
Postoperative wound infection	1 (3)	0	0	1 (1)
Pseudomonas infection	1 (3)	0	0	1 (1)
Stitch abscess	1 (3)	0	0	1 (1)
Urinary tract infection	1 (3)	1 (3)	0	2 (2)
Injury, poisoning and procedural complications	5 (13)	1 (3)	4 (11)	10 (9)
Fall	0	0	1 (3)	1 (1)
Femur fracture	1 (3)	0	1 (3)	2 (2)
Forearm fracture	1 (3)	0	0	1 (1)
Fracture displacement	2 (5)	0	2 (6)	4 (4)
Head injury	0	1 (3)	0	1 (1)
Procedural pain	2 (5)	0	0	2 (2)
Investigations	1 (3)	1 (3)	1 (3)	3 (3)
Blood amylase increased	0	0	1 (3)	1 (1)
Body temperature increased	0	1 (3)	0	1 (1)
International normalised ratio increased	1 (3)	0	0	1 (1)
Metabolism and nutrition disorders	2 (5)	2 (6)	2 (6)	6 (6)
Dehydration	1 (3)	1 (3)	1 (3)	3 (3)
Hyperglycaemia	0	0	1 (3)	1 (1)
Hyperkalaemia	1 (3)	0	0	1 (1)
Hypovolaemia	1 (3)	1 (3)	0	2 (2)
Musculoskeletal and connective tissue disorders	2 (5)	5 (14)	1 (3)	8 (7)
Arthralgia	0	1 (3)	0	1 (1)
Groin pain	0	1 (3)	0	1 (1)
Muscular weakness	0	1 (3)	0	1 (1)
Osteoarthritis	0	1 (3)	1 (3)	2 (2)
Osteonecrosis	1 (3)	2 (6)	0	3 (3)
Pain in extremity	1 (3)	0	0	1 (1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (8)	1 (3)	4 (11)	8 (7)
Basal cell carcinoma	0	0	1 (3)	1 (1)
Bowen's disease	0	0	1 (3)	1 (1)
Breast cancer	1 (3)	0	0	1 (1)
Colon neoplasm	1 (3)	0	0	1 (1)
Prostate cancer	0	1 (3)	0	1 (1)
Squamous cell carcinoma	0	0	1 (3)	1 (1)
Squamous cell carcinoma of skin	0	0	1 (3)	1 (1)
Squamous cell carcinoma of the cervix	1 (3)	0	0	1 (1)
Nervous system disorders	3 (8)	1 (3)	2 (6)	6 (6)
Cerebral atrophy	0	1 (3)	0	1 (1)
Cerebrovascular accident	0	0	2 (6)	2 (2)
Dementia	0	0	1 (3)	1 (1)
Epilepsy	1 (3)	0	0	1 (1)
Syncope	2 (5)	0	0	2 (2)

Table 5. Number (%) of Subjects Reporting Treatment-Emergent Serious Adverse Events

System Organ Class [a] Preferred Term	Treatment: Standard of Care Control n=38	Treatment: 1.0 mg/mL rhBMP-2/CPM Acute n=35	Treatment: 2.0 mg/mL rhBMP-2/CPM Acute n=35	Total n=108
Psychiatric disorders	1 (3)	0	1 (3)	2 (2)
Mental status changes	1 (3)	0	0	1 (1)
Psychotic disorder	0	0	1 (3)	1 (1)
Renal and urinary disorders	2 (5)	0	1 (3)	3 (3)
Renal failure	1 (3)	0	0	1 (1)
Renal failure acute	1 (3)	0	1 (3)	2 (2)
Respiratory, thoracic and mediastinal disorders	7 (18)	2 (6)	2 (6)	11 (10)
Acute respiratory failure	1 (3)	0	0	1 (1)
Chronic obstructive pulmonary disease	1 (3)	1 (3)	0	2 (2)
Cough	1 (3)	0	0	1 (1)
Dyspnoea	0	0	1 (3)	1 (1)
Hydrothorax	1 (3)	0	0	1 (1)
Hypoxia	1 (3)	0	0	1 (1)
Pulmonary embolism	3 (8)	1 (3)	1 (3)	5 (5)
Tachypnoea	0	0	1 (3)	1 (1)
Skin and subcutaneous tissue disorders	1 (3)	1 (3)	0	2 (2)
Decubitus ulcer	1 (3)	0	0	1 (1)
Erythema	0	1 (3)	0	1 (1)
Surgical and medical procedures	1 (3)	0	0	1 (1)
Medical device removal	1 (3)	0	0	1 (1)
Vascular disorders	4 (11)	2 (6)	0	6 (6)
Deep vein thrombosis	2 (5)	2 (6)	0	4 (4)
Haematoma	1 (3)	0	0	1 (1)
Peripheral circulatory failure	1 (3)	0	0	1 (1)
Venous insufficiency	0	1 (3)	0	1 (1)

Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
Abbreviations: CPM=calcium phosphate matrix; rhBMP-2=recombinant human bone morphogenetic protein-2.

a. Totals for the No. of Subjects at a higher level are not necessarily the sum of those at the lower levels since a subject may report two or more different adverse events within the higher level category.

One (1) subject each from the SOC group and the 1.0 mg/mL rhBMP-2/CPM treatment group were withdrawn from the study due to AEs of osteonecrosis. Both subjects had displaced femoral neck fractures which is a risk factor for osteonecrosis.

Three (3, 8%) subjects in the SOC group, 1 (3%) subject from the 1.0 mg/mL rhBMP-2/CPM treatment group and 4 (11%) subjects from the 2.0 mg/mL rhBMP-2/CPM treatment group reported malignancies. No potential treatment effect in the incidence of malignancies could be identified.

Given the population characteristics and the trauma that hip fracture patients suffer, death is not an unexpected outcome. Fifteen (15) subjects died during this study: 3 subjects (8%) in the SOC treatment group, 6 subjects (17%) in the 1.0 mg/mL rhBMP-2/CPM treatment group

and 6 subjects (17%) in the 2.0 mg/mL rhBMP-2/CPM treatment group. None of the reported deaths were deemed related to the treatment or to the protocol.

Meaningful and potential causally related differences in laboratory measurements between the SOC group and the active groups were not observed.

Results of Other Analyses: At least 94% of the surgeons considered test article preparation, ease of injecting and ability to inject entire volume to be satisfactory, at least 83% of surgeons considered localization relative to fracture site using fluoroscopy to be satisfactory and 69% of surgeons considered identification relative to fracture site using fluoroscopy to be satisfactory.

CONCLUSION(S): rhBMP-2/CPM was generally well tolerated at the doses of 1.0 mg/mL and 2.0 mg/mL and was feasible to inject at volumes up to 5.0 mL. However, noninferiority in the incidence of secondary fracture displacement was not assumed in the 1.0 mg/mL rhBMP-2/CPM treatment group when the difference in proportions 95% CI was pooled or in the 2.0 mg/mL treatment group when the difference in proportions 95% CI was adjusted for femoral neck/interchanteric strata. The evaluation of rhBMP-2/CPM in subjects with proximal femur fractures did not demonstrate a positive risk/benefit ratio to justify its use as an adjunct to internal fixation. Current SOC, using arthroplasty to treat displaced, unstable fractures seems therefore more appropriate. The clinical development of rhBMP-2/CPM for the treatment of proximal femoral fractures in particular has been stopped.