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GENERIC DRUG NAME and/or COMPOUND NUMBER:

Recombinant human bone morphogenetic protein-2/calcium phosphate matrix (rhBMP-2/CPM)/WAY-205074

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: Not Applicable

NATIONAL CLINICAL TRIAL NO.: NCT00387686

PROTOCOL NO.: B1921003 (3100N7-210-WW)

PROTOCOL TITLE: A Phase 2/3, Multicenter, Double-blind, Randomized, Controlled Study of Recombinant Human Bone Morphogenetic Protein-2 (rhBMP-2)/Calcium Phosphate Matrix (CPM) in Closed Diaphyseal Tibial Fractures.

Study Centers: This was a multicenter trial conducted in 91 investigational sites in 18 countries.

Study Initiation Date and Primary Completion or Completion Dates:
29 November 2006 to 30 March 2010

The study was terminated prematurely.

Phase of Development: Phase 2/3

Study Objectives:
Primary objective
To demonstrate that a single dose of rhBMP-2/CPM administered at the fracture site via percutaneous injection in combination with the standard of care (SOC: definitive fracture fixation within 72 hours after injury by means of a locked, reamed intramedullary (IM) nail) would accelerate fracture union and return to normal function in subjects with closed diaphyseal tibial fracture when compared to SOC alone.

This primary objective would be established if the study met the following 2 co-primary endpoints:
1. Demonstration that rhBMP-2/CPM reduced the time to fracture union compared to SOC alone, based on radiographic assessments by an independent central evaluation committee (CEC).
2. Demonstration that rhBMP-2/CPM accelerated the return to normal function compared to SOC alone based on assessment of time to full weight bearing without pain at the fracture site as established by an investigator masked to therapy assignment.

The study hypothesis was that the mean time to fracture union and to pain-free full weight bearing would be reduced by at least 4 weeks in subjects with closed diaphyseal tibia fractures who received 5.0 mL of rhBMP-2/CPM (1.0 or 2.0 mg/mL) as an adjuvant treatment, when compared to subjects who received only the SOC.

Secondary objectives
1. Demonstrate the overall safety of rhBMP-2/CPM administration, particularly based on key safety outcomes (venous thromboembolic events, compartment syndrome, infection in the region under study [RUS], delayed fracture union and nonunion, and hardware failure (HWF).

METHODS

Study Design: This study was a phase 2/3, multicenter, double-blind, randomized, parallel dose, controlled, efficacy, safety, and feasibility study of two concentrations of rhBMP-2/CPM as adjuvant therapy for subjects who sustained a closed diaphyseal tibial fracture treated surgically with a reamed, locked, IM nail. All subjects should have received the surgical treatment within 72 hours after the injury. Subjects' physical rehabilitation was to be conducted according to the site's rehabilitation program. Although originally planned as a 600-subject study, the study was terminated after the conduct of a planned interim analysis at a time that 387 subjects had been randomized

Subjects were randomly assigned to 1 of 4 treatment groups in a ratio of 2:2:1:1. The investigator who operated on the fracture was masked to randomized treatment assignment at the "injected group" level. The CEC and the investigator, who assessed weight bearing, were masked to all 4 treatment assignments:

1.0 mg/mL rhBMP-2/CPM + SOC
2.0 mg/mL rhBMP-2/CPM + SOC
Buffer/CPM + SOC
SOC alone

Injection of rhBMP-2/CPM in the two treatment groups occurred in the operating room at the time of definitive fracture fixation. Follow-up was to occur at 2, 4, 8, 12, 16, 20, 26, 39, and 52 weeks after administration of the randomized treatment assignment. Because the study was prematurely terminated, subjects were discontinued from the study and did not perform all planned follow-up visits.

Number of Subjects (Planned and Analyzed): Six hundred (600) subjects were planned to be enrolled. A total of 369 subjects were analyzed for safety.

Diagnosis and Main Criteria for Inclusion: Subjects (men and non-pregnant, non-nursing women) aged ≥18 years; skeletally mature with closed diaphyseal tibial fracture (Orthopaedic Trauma Association classifications 42A, 42B, or 42C) to be treated with closed reduction and definitive internal fracture fixation by means of a reamed, locked IM nail within 72 hours after injury (SOC) were enrolled.

Study Treatment: Subjects were randomly assigned to 1 of 4 treatment groups in 2:2:1:1 ratio as described above. The rhBMP-2 or buffer solution was to be mixed with the CPM powder to form a paste-like material. Within 15 minutes after the preparation, a total volume of 5.0 mL (± 1 mL) of rhBMP-2/CPM was to be injected percutaneously within the fracture fragments, intraosseously or along the fracture cortex perioseously, under fluoroscopic guidance, after definitive fracture reduction and fixation with the reamed and locked IM nail was completed. When administering rhBMP-2/CPM, the main objective was to ensure that it was in direct contact with the fracture.

Efficacy Evaluations: Evaluation of efficacy was based on the following:
Radiographic evidence of fracture union, defined as bridging callus or disappearance of the fracture line(s) on atleast 3 of 4 diaphyseal aspects of orthogonal radiographs, assessed by the CEC. Bridging callus was defined as the appearance of mineralized callus, spanning the proximal and distal fracture fragments. Bridging callus was to be sufficiently mineralized such that it remained visible on follow-up radiographs, without regression, thereby supporting the diagnosis of "fracture union." Obliteration of the fracture lines referred to endosteal bone remodeling and should not have been mistaken with obliteration by non-bony substances (eg, CPM).

Treatment success for radiographic fracture union included subjects with fractures that:

- were radiographically united as defined above,
- did not require an intervention that altered (promoted or delayed) fracture union, and
- did not sustain HWF which resulted in self-dynamization.

Treatment success for the ability to bear full weight on the affected limb included subjects who could walk 6 meters without the use of an assistive device, other than to maintain balance thereby bearing full weight, without experiencing pain at the fracture site.

Immunogenicity Evaluations: Blood samples were collected at baseline and at the visits scheduled for 8, 20, and 39 weeks to assess the prevalence and incidence of anti-BMP-2 antibody formation using a validated enzyme-linked immunosorbent assay (ELISA). Neutralizing anti-BMP-2 antibodies assays were performed on samples that had reactivity in the baseline assay for antibodies to BMP-2.

Safety Evaluations: Safety was determined using the following assessments: monitoring of adverse events (AEs) and serious adverse events (SAEs), concomitant medications, vital sign measurements, physical examination of the limb under study, investigator's assessment of radiographs of the fractured tibia to assess fracture-related complications, routine hematology and chemistry laboratory tests, and BMP-2 antibody testing.

Safety was established if the overall safety and particularly the following local and systemic safety outcomes in the active treatment groups were comparable in rate of occurrence, clinical characteristics, and severity to those of the SOC control group: Venous thromboembolic events, such as deep vein thrombosis and pulmonary embolism, compartment syndrome, infection of the RUS, delayed fracture union and nonunion and HWF.

Other Evaluations: The feasibility of rhBMP-2/CPM administration was evaluated using an investigator satisfaction questionnaire and a radiographic comparison to verify whether the rhBMP-2/CPM remained localized at the injection site.

Statistical Methods: Efficacy analyses were performed for the intent-to-treat (ITT) population defined as all subjects who had received a treatment assignment and who were not subsequently withdrawn and replaced before treatment. The primary efficacy analysis was conducted to detect a 4-week decrease in the median time to fracture healing when comparing SOC alone versus rhBMP-2/CPM plus SOC, using the log-rank test statistic with 85% power at α=0.05 (2-sided). The sample size estimation was 600 subjects assuming a fixed follow-up of 1 year for each subject and 6 subjects enrolled per week. An interim analysis was planned for an independent data monitoring committee (DMC) to review unblinded safety and efficacy data of 180 subjects followed for 6 months.

RESULTS

The interim analysis planned in the protocol was conducted in March 2009. An independent data monitoring committee (DMC) reviewed unblinded safety and efficacy data of 180 subjects followed for 6 months. Recommendation was made to stop the rhBMP-2/CPM 2.0 mg/mL treatment arm for futility because a delay in radiographic union was observed in this treatment arm compared to SOC (median increase of 3.7 weeks). The p-value boundary for which enrollment was to be stopped for a rhBMP-2/CPM treatment arm was 0.476. The observed p-value comparing the SOC arm to the rhBMP-2/CPM 2.0 mg/mL treatment arm was 0.946, which led to the DMC recommendation to stop enrollment in this arm.

Given that the high dose of rhBMP-2/CPM was deemed ineffective, it was unexpected that the lower dose of rhBMP-2/CPM would be effective. The protocol was amended to allow summary data from the planned interim analysis to be unblinded to sponsor Senior Management. As the chance of a successful outcome for the 1.0 mg/mL treatment group was deemed small, the decision was made to terminate the study on 17 June 2009. The last subject enrolled into the study on 08 April 2009. When the decision was made to terminate the study, subjects in follow-up were prematurely discontinued from the study by the sponsor, except in United Kingdom where subjects were to be followed for 52 weeks as planned in the flowchart upon request of the Medical Health products Regulatory Agency. However, with the agreement of health authorities of all the other countries participating in the study, the sponsor offered prematurely discontinued subjects to be followed for safety according to a Patient Management Plan.

This PhRMA web synopsis summarizes key safety and efficacy results and the feasibility of rhBMP-2/CPM administration; results of the remaining secondary and exploratory analyses are not provided in this web synopsis.

Subject Disposition and Demography: Sixty-two (62) subjects were randomized and treated in the SOC only treatment group, 60 subjects in the buffer/CPM treatment group, 122 subjects in the 1mg/mL rhBMP-2/CPM treatment group and 125 subjects in the 2mg/mL rhBMP-2/CPM treatment group. Disposition of subjects is present in Table 1.

Table 1: Summary of Subject Disposition

	Treatment				
	Standard of Care Control	**Buffer/CPM Acute**	**1.0 mg/mL rhBMP-2/CPM Acute**	**2.0 mg/mL rhBMP-2/CPM Acute**	**Total**
Screened					392
Randomized	63	62	128	134	387
Discontinued and Replaced Subjects	1 (2)	2 (3)	6 (5)	9 (7)	18 (5)
Treated	60 (95)	60 (97)	121 (95)	123 (92)	364 (94)
Randomized Treatment Not Received	2 (3)[a]	0	1 (<1)	2 (1)	5 (1)
Early Conclusion	26 (41)	23 (37)	59 (46)	60 (45)	168 (43)
Adverse Event	1 (2)	0	0	0	1 (<1)
Subject Request	9 (14)	6 (10)	12 (9)	10 (7)	37 (10)
Investigator Request	0	1 (2)	3 (2)	4 (3)	8 (2)
Death	0	0	1 (<1)	0	1 (<1)
Discontinuation of Study by Sponsor	6 (10)	11 (18)	18 (14)	23 (17)	58 (15)
Lost to Follow-up	9 (14)	3 (5)	19 (15)	20 (15)	51 (13)
Noncompliance	0	0	1 (<1)	0	1 (<1)
Other	1 (2)	2 (3)	5 (4)	3 (2)	11 (3)
Completed Study	37 (59)	39 (63)	69 (54)	74 (55)	219 (57)

CPM=calcium phosphate matrix; rhBMP-2=recombinant human bone morphogenetic protein-2; SOC=standard of care; a) These 2 subjects actually received SOC.
Treated: An enrolled subject who has received the randomized treatment assignment.

The study population consisted of 101 (27%) female and 268 (73%) male subjects aged 18 to 80 years, with a mean age of 39 years. Minor differences 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

Characteristic	Treatment				
	Standard of Care Control (n = 62)	Buffer/CPM Acute (n = 60)	1.0 mg/mL rhBMP-2/CPM Acute (n = 122)	2.0 mg/mL rhBMP-2/CPM Acute (n = 125)	Total (n = 369)
Age (years)					
N	62	60	122	125	369
Mean	39.55	39.55	38.66	38.89	39.03
Standard Deviation	14.74	14.68	14.38	13.89	14.27
Minimum	18.00	18.00	18.00	18.00	18.00
Maximum	80.00	73.00	76.00	77.00	80.00
Median	38.00	38.00	37.00	40.00	38.00
Sex, N (%)					
Female	23 (37)	23 (38)	23 (19)	32 (26)	101 (27)
Male	39 (63)	37 (62)	99 (81)	93 (74)	268 (73)
Race, N (%)					
White	47 (76)	44 (73)	89 (73)	95 (76)	275 (75)
Black	2 (3)	3 (5)	7 (6)	6 (5)	18 (5)
Other	13 (21)	13 (22)	26 (21)	24 (19)	76 (21)
Height (cm)					
N	62	59	122	125	368
Mean	170.94	170.45	173.26	173.22	172.41
Standard Deviation	10.72	8.60	10.78	9.64	10.10
Minimum	145.00	152.40	147.30	152.00	145.00
Maximum	194.00	195.60	195.60	200.70	200.70
Median	171.50	170.20	174.00	172.70	172.00
Missing	0	1	0	0	1
Weight (kg)					
N	62	60	122	125	369
Mean	76.32	77.68	78.00	80.19	78.41
Standard Deviation	22.88	16.47	16.29	19.07	18.49
Minimum	44.00	45.40	45.00	48.00	44.00
Maximum	184.00	129.70	129.30	147.40	184.00
Median	74.80	75.00	75.50	75.50	75.00
Tobacco Use, N (%)					
No	40 (65)	36 (60)	77 (63)	80 (64)	233 (63)
Yes	22 (35)	24 (40)	45 (37)	45 (36)	136 (37)

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

Baseline fracture and injury characteristics were well balanced and therefore, are not deemed to have affected the safety outcomes. Baseline fracture and injury characteristics are presented in Table 3.

Table 3: Summary of Baseline Fracture and Injury Characteristics

	Treatment				
Characteristics	**Standard of Care Control (n = 62)**	**Buffer/CPM Acute (n = 60)**	**1.0 mg/mL rhBMP-2/CPM Acute (n = 122)**	**2.0 mg/mL rhBMP-2/CPM Acute (n = 125)**	**Total (n = 369)**
Mechanism of Injury					
Motor vehicle accident	11 (18)	14 (23)	23 (19)	28 (22)	76 (21)
Motorcycle accident	11 (18)	4 (7)	21 (17)	13 (10)	49 (13)
Fall from standing height or less	18 (29)	25 (42)	41 (34)	37 (30)	121 (33)
Fall from greater than standing height	6 (10)	2 (3)	13 (11)	14 (11)	35 (9)
Sporting injury	13 (21)	13 (22)	18 (15)	23 (18)	67 (18)
Other	3 (5)	2 (3)	6 (5)	10 (8)	21 (6)
Tibia Under Study					
Left	32 (52)	27 (45)	51 (42)	54 (43)	164 (44)
Right	30 (48)	33 (55)	71 (58)	71 (57)	205 (56)
Fracture Location					
Proximal 1/3	3 (5)	1 (2)	2 (2)	3 (2)	9 (2)
Proximal-middle 1/3	2 (3)	3 (5)	3 (2)	8 (6)	16 (4)
Middle 1/3	14 (23)	12 (20)	30 (25)	29 (23)	85 (23)
Middle-distal 1/3	15 (24)	22 (37)	49 (40)	43 (34)	129 (35)
Distal 1/3	27 (44)	21 (35)	38 (31)	42 (34)	128 (35)
Missing	1 (2)	1 (2)	0	0	2 (1)
Tscherne Classification					
C0	28 (45)	24 (40)	56 (46)	55 (44)	163 (44)
C1	28 (45)	31 (52)	54 (44)	57 (46)	170 (46)
C2	2 (3)	4 (7)	10 (8)	8 (6)	24 (7)
C3	2 (3)	1 (2)	1 (1)	3 (2)	7 (2)
Missing	2 (3)	0	1 (1)	2 (2)	5 (1)
OTA Classification[a]					
42A Unifocal Fractures	35 (56)	38 (63)	76 (62)	65 (52)	214 (58)
42B Wedge Fractures	23 (37)	17 (28)	41 (34)	45 (36)	126 (34)
42C Complex Fractures	3 (5)	4 (7)	4 (3)	13 (10)	24 (7)
Not evaluated	1 (2)	0	0	0	1 (0)
Missing	0	1 (2)	1 (1)	2 (2)	4 (1)
Fractures Sustained					
Isolated Tibia[b]	54 (87)	53 (88)	106 (87)	96 (77)	309 (84)
No Other Fractures but with Other Injuries	4 (6)	1 (2)	8 (7)	13 (10)	26 (7)
Other Fractures	4 (6)	6 (10)	8 (7)	16 (13)	34 (9)
Concurrent Injuries					
Injuries	51 (82)	51 (85)	97 (80)	91 (73)	290 (79)
No Injuries	11 (18)	9 (15)	25 (20)	34 (27)	79 (21)

CEC=central evaluation committee; CPM=calcium phosphate matrix; OTA=Orthopaedic Trauma Association; rhBMP-2=recombinant human bone morphogenetic protein-2.
a: The OTA classification is assessed by the CEC
b.: Isolated tibia is a unilateral tibia facture with no other fractures (excluding ipsilateral fibula fracture) and no other injuries (except blood loss requiring transfusion and lacerations, abrasions and contusions).

Efficacy Results: The proportion of the subjects who reached fracture union was comparable between groups. Despite a median delay in radiographic union of 2.8 weeks in the 2.0 mg/mL rhBMP-2/CPM group compared to the SOC, the distribution of the time to radiographic healing was not statistically different between the two groups (Table 4).

Table 4: Comparison of Time (Weeks) to Radiographic Fracture Union in rhBMP-2 Treatment Groups Versus Standard of Care and rhBMP-2 Treatment Groups Versus Buffer/CPM in the Intent-to-Treat Population

	Standard of Care Control (n = 62)	Buffer/CPM Acute (n = 60)	1.0 mg/mL rhBMP-2/CPM Acute (n = 122)	2.0 mg/mL rhBMP-2/CPM Acute (n = 125)
No of subjects achieving union	54 (91.5%)	50 (86.2%)	103 (88.8%)	107 (88.4%)
No. of censored subjects	5 (8.5%)	8 (13.8%)	13 (11.2%)	14 (11.6%)
Q1 time to union (95% CI)	12.3 (12.0, 12.6)	12.4 (11.9, 13.0)	12.0 (11.9, 12.4)	12.4 (12.3, 13.0)
Median time to union (95% CI)	13.1 (12.6, 16.1)	15.4 (13.0, 16.3)	13.0 (12.6, 14.3)	15.9 (13.4, 16.4)
Q3 time to union (95% CI)	17.0 (15.4, 20.4)	19.4 (16.3, 21.6)	16.4 (15.9,17.0)	18.3 (17.0,20.0)
Time to first union	7.3	7.6	7.3	8.4
Time to last union	52.0	52.0	36.0	54.3
rhBMP-2 Treatment Groups versus standard of Care				
Change in median time : Reference standard of care (b)			-0.1	2.7
Log rank p value : Reference standard of care (c)			0.3005	0.3704
Hazard ratio : Reference standard of care			1.190	0.866
rhBMP-2 Treatment Groups Versus Buffer/CPM				
Change in median time : Reference standard of care (b)			-2.4	0.4
Log rank p value : Reference standard of care (c)			0.0364	0.7288
Hazard ratio : Reference standard of care			1.453	1.056

(a) Subject outcome is one of the following: self-dynamization; fracture healing intervention; withdrawn from study; lost to follow-up; or no result at study completion; (b) Formula for Median Change: rhBMP-2/CPM minus Reference; (c) Only consider 1.0 mg/mL rhBMP-2/CPM comparison if 2.0 mg/mL rhBMP-2/CPM comparison significant at 5% level

At the time of the final analysis, 80% of the subjects on average had the ability to bear their full weight on the affected limb without pain. None of the rhBMP-2 groups accelerated the time to pain-free full weight bearing. The results of full-weight bearing analysis for the ITT population are summarized in Table 5.

Table 5: Comparison of Time to Pain-Free Full Weight Bearing (PFFWB) in rhBMP-2 Treatment Groups versus standard of Care and rhBMP-2 Treatment Groups versus Buffer/CPM in the Intent-to-Treat Population

	Standard of Care Control (n = 62)	Buffer/CPM Acute (n = 60)	1.0 mg/mL rhBMP-2/CPM Acute (n = 122)	2.0 mg/mL rhBMP-2/CPM Acute (n = 125)
No of Subjects Achieving PFFWB during ambulation	48 (78.7%)	48 (81.4%)	96 (80.7%)	108 (87.8%)
No. of Censored subjects (b)	13 (21.3%)	11 (18.6%)	23 (19.3%)	15 (12.2%)
Q1 time to PFFWB during ambulation (95 % CI)	9.0 (8.1, 12.3)	11.3 (8.1, 13.0))	8.9 (8.4, 11.1)	11.1 (9.0, 12.4)
Median time to PFFWB during ambulation (95 % CI)	13.4 (12.6, 17.0)	16.4 (13.0, 20.4)	13.4 (12.1, 16.9)	14.3 (12.9, 16.4)
Q3 time to PFFWB during ambulation (95 % CI)	21.4 (17.0, 39.3)	39.0 (20.4, 40.7)	21.6 (19.9,26.6)	22.3 (17.0,26.1)
Time to first PFFWB during ambulation	4.0	4.3	3.6	4.0
Time to last PFFWB during ambulation	53.3	52.4	51.9	54.3
rhBMP-2 Treatment Groups versus standard of Care				
Change in median time : Reference standard of care (c)			0.0	0.9
Log rank p value : Reference standard of care (d)			0.6597	0.8146
Hazard ratio : Reference standard of care			1.078	1.043
rhBMP-2 Treatment Groups versus Buffer/CPM				
Change in median time : Reference standard of care (c)			-3.0	-2.1
Log rank p value : Reference standard of care (d)			0.1371	0.1869
Hazard ratio : Reference standard of care			1.300	1.249

(a) Ethics committee did not approve protocol amendment at the time of analysis; one site removed.
(b) Subject outcome is one of the following: self-dynamization; fracture healing intervention; withdrawn from study; lost to follow-up; or no result at study completion.
(c) Formula for Median Change: rhBMP-2/CPM minus Reference.
(d) Only consider 1.0 mg/mL rhBMP-2/CPM comparison if 2.0 mg/mL rhBMP-2/CPM comparison significant at 5% level

Safety Results: One (1) subject in the 1.0 mg/mL rhBMP-2 treatment group, who had a history of phlebitis, hypertension, and hyperlipidemia, died during the study. Eight (8) days after fracture fixation and rhBMP-2 administration, the subject died as a result of pulmonary embolism. An autopsy revealed that the thrombus originated in the contralateral limb.

Serious Adverse Events (SAEs) were reported for 8 (13%) subjects in the SOC treatment group, compared to 14 (23%) subjects in the buffer/CPM treatment group, and 22 (18%) subjects in each of the 2 rhBMP-2/CPM treatment groups (Table 6).

Table 6: Number (%) of Subjects Reporting Related Treatment-Emergent Serious Adverse Events

	Treatment				
System Organ Class [a] Preferred Term	**Standard of Care Control n=62**	**Buffer/CPM Acute n=60**	**1.0 mg/mL rhBMP-2/CPM Acute n=122**	**2.0 mg/mL rhBMP-2/CPM Acute n=125**	**Total n=369**
Any Adverse Event	0	4 (7)	7 (6)	7 (6)	18 (5)
General disorders and administration site conditions	0	1 (2)	3 (2)	1 (1)	5 (1)
Injection site discharge	0	0	0	1 (1)	1 (0)
Injection site inflammation	0	0	1 (1)	0	1 (0)
Oedema	0	0	1 (1)	0	1 (0)
Oedema peripheral	0	1 (2)	1 (1)	0	2 (1)
Infections and infestations	0	1 (2)	0	2 (2)	3 (1)
Device related infection	0	0	0	1 (1)	1 (0)
Osteomyelitis	0	1 (2)	0	0	1 (0)
Sepsis	0	0	0	1 (1)	1 (0)
Injury, poisoning and procedural complications	0	0	1 (1)	0	1 (0)
Traumatic haematoma	0	0	1 (1)	0	1 (0)
Musculoskeletal and connective tissue disorders	0	1 (2)	4 (3)	2 (2)	7 (2)
Compartment syndrome	0	1 (2)	3 (2)	1 (1)	5 (1)
Fracture nonunion	0	0	0	1 (1)	1 (0)
Pain in extremity	0	0	1 (1)	0	1 (0)
Pregnancy, puerperium and perinatal conditions	0	0	0	1 (1)	1 (0)
Abortion spontaneous	0	0	0	1 (1)	1 (0)
Skin and subcutaneous tissue disorders	0	1 (2)	1 (1)	0	2 (1)
Erythema	0	0	1 (1)	0	1 (0)
Skin exfoliation	0	1 (2)	0	0	1 (0)
Surgical and medical procedures	0	1 (2)	0	0	1 (0)
Abscess drainage	0	1 (2)	0	0	1 (0)
Vascular disorders	0	0	1 (1)	2 (2)	3 (1)
Deep vein thrombosis	0	0	1 (1)	2 (2)	3 (1)

CPM=calcium phosphate matrix; rhBMP-2=recombinant human bone morphogenetic protein-2.
Classifications of adverse events are based on the Medical Dictionary for Regulatory Activities (MedDRA).
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 2 or more different adverse events within the higher level category.

One subject in the SOC group withdrew consent during follow-up period due to a psychotic disorder. The TEAEs reported by more than 10% of the subjects are presented in Table 7.

Table 7: Number (%) of Subjects Reporting Treatment-Emergent Adverse Events in More Than 10% of Subjects

System Organ Class [a] Preferred Term	Standard of Care Control n=62	Buffer/CPM Acute n=60	1.0 mg/mL rhBMP-2/CPM Acute n=122	2.0 mg/mL rhBMP-2/CPM Acute n=125	Total n=369
Any Adverse Event	59 (95)	57 (95)	111 (91)	116 (93)	343 (93)
Blood and lymphatic system disorders	3 (5)	6 (10)	6 (5)	10 (8)	25 (7)
Gastrointestinal disorders	12 (19)	15 (25)	27 (22)	29 (23)	83 (22)
Constipation	4 (6)	7 (12)	15 (12)	11 (9)	37 (10)
Nausea	4 (6)	5 (8)	13 (11)	14 (11)	36 (10)
General disorders and administration site conditions	25 (40)	26 (43)	62 (51)	62 (50)	175 (47)
Oedema peripheral	9 (15)	9 (15)	22 (18)	16 (13)	56 (15)
Pyrexia	5 (8)	7 (12)	27 (22)	21 (17)	60 (16)
Infections and infestations	11 (18)	10 (17)	21 (17)	15 (12)	57 (15)
Injury, poisoning and procedural complications	20 (32)	27 (45)	48 (39)	60 (48)	155 (42)
Fracture[b]	8 (13)	10 (17)	17 (14)	19 (15)	54 (15)
Postoperative heterotopic calcification	1 (2)	9 (15)	22 (18)	22 (18)	54 (15)
Investigations	41 (66)	40 (67)	82 (67)	94 (75)	257 (70)
Aspartate aminotransferase increased	12 (19)	9 (15)	15 (12)	25 (20)	61 (17)
Blood calcium decreased	14 (23)	14 (23)	19 (16)	34 (27)	81 (22)
Blood glucose increased	11 (18)	10 (17)	28 (23)	29 (23)	78 (21)
Blood lactate dehydrogenase increased	5 (8)	6 (10)	10 (8)	11 (9)	32 (9)
Blood phosphorus decreased	1 (2)	5 (8)	9 (7)	17 (14)	32 (9)
Carbon dioxide decreased	11 (18)	13 (22)	34 (28)	30 (24)	88 (24)
Haematocrit decreased	8 (13)	18 (30)	12 (10)	26 (21)	64 (17)
Haemoglobin decreased	14 (23)	18 (30)	18 (15)	28 (22)	78 (21)
Metabolism and nutrition disorders	21 (34)	29 (48)	47 (39)	41 (33)	138 (37)
Hyperglycaemia	10 (16)	16 (27)	25 (20)	24 (19)	75 (20)
Hypocalcaemia	6 (10)	9 (15)	18 (15)	19 (15)	52 (14)
Hypophosphataemia	8 (13)	6 (10)	16 (13)	9 (7)	39 (11)
Musculoskeletal and connective tissue disorders	23 (37)	33 (55)	54 (44)	57 (46)	167 (45)
Arthralgia	6 (10)	11 (18)	21 (17)	16 (13)	54 (15)
Pain in extremity	13 (21)	14 (23)	24 (20)	27 (22)	78 (21)
Nervous system disorders	18 (29)	15 (25)	29 (24)	42 (34)	104 (28)
Headache	7 (11)	5 (8)	10 (8)	14 (11)	36 (10)
Psychiatric disorders	6 (10)	5 (8)	16 (13)	16 (13)	43 (12)
Respiratory, thoracic and mediastinal disorders	15 (24)	20 (33)	38 (31)	39 (31)	112 (30)
Hypocapnia	12 (19)	16 (27)	26 (21)	31 (25)	85 (23)
Skin and subcutaneous tissue disorders	12 (19)	15 (25)	39 (32)	42 (34)	108 (29)
Erythema	10 (16)	8 (13)	28 (23)	29 (23)	75 (20)
Vascular disorders	6 (10)	3 (5)	13 (11)	12 (10)	34 (9)

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 because a subject may report 2 or more different adverse events within the higher level category.
b. The vast majority of fracture cases were reported as "fracture site tenderness," which consequently mapped

Table 7: Number (%) of Subjects Reporting Treatment-Emergent Adverse Events in More Than 10% of Subjects

System Organ Class [a] Preferred Term	Standard of Care Control n=62	Buffer/CPM Acute n=60	1.0 mg/mL rhBMP-2/CPM Acute n=122	2.0 mg/mL rhBMP-2/CPM Acute n=125	Total n=369

in MedDRA to "fracture" although an occasional event of a subsequent fracture outside the RUS or "fracture site swelling" or "fracture site pain" mapped to "fracture."

Key Safety outcomes:

A total of 250 (68%) subjects had at least 1 TEAE in the RUS. The most common TEAEs in the RUS were erythema, pain in extremity (64 subjects, 17%), fracture, oedema peripheral and postoperative heterotopic calcification, and arthralgia (43 subjects, 12%). With the exception of postoperative heterotopic ossification/calcification, no treatment effect could be identified.

Postoperative heterotopic ossification/calcification

Postoperative heterotopic ossification/calcification and calcinosis in the RUS were reported for 1 (2%) subject in the SOC treatment group, 9 (15%) subjects in the buffer/CPM treatment group, 23 (19%) subjects in the 1.0 mg/mL rhBMP-2/CPM treatment group, and 24 (19%) subjects in the 2.0 mg/mL rhBMP-2/CPM treatment group. As investigators were to report visible test article as postoperative heterotopic calcification, most likely, early onset indicated presence of CPM paste, rather than actual heterotopic ossification. Furthermore, onset of late stage heterotopic calcification was relatively rare, although it could not be concluded from the data whether several subjects had reported visible test article at study conclusion or heterotopic ossification. No other related adverse events were reported in association with postoperative heterotopic calcification, which is listed as a risk of rhBMP-2.

Venous thromboembolic events

Thromboembolic events, including pulmonary embolism, vascular disorders venous, and thrombosis of the limb, were only reported in the "injected treatment groups" by 1 (2%) subject in the buffer/CPM treatment group, 5 (4%) subjects in the 1.0 mg/mL rhBMP-2/CPM treatment group, and 4 (3%) subjects in the 2.0 mg/mL rhBMP-2/CPM treatment group. One (1) subject in the 1.0 mg/mL rhBMP-2 treatment died from pulmonary embolism during this study. This death was considered not to be related to rhBMP-2/CPM. All the venous thromboembolic events were reported as SAEs except for 1 subject who received 1.0 mg/mL rhBMP-2/CPM. Although venous thromboembolic events only occurred in the rhBMP-2/CPM injected treatment groups, it is a relatively common occurrence in the trauma setting. The difference among treatment groups was not statistically significant.

Compartment syndrome

Compartment syndrome is a relatively common event after lower limb trauma and was experienced similarly in the 4 groups: 1 (2%) subject in the SOC group, 2 (3%) subjects in the buffer/CPM treatment group, 4 (3%) subjects in the 1.0 mg/mL treatment group, and 2 (2%) subjects in the 2.0 mg/mL treatment group. All subjects with CS in the injected

treatment group developed severe or very severe compartment syndromes. The outcome of compartment syndrome after fasciotomy was not different among the treatment groups.

Infection of the region under study [RUS]
The overall incidence of infections in the RUS and sepsis was similar between the 4 treatment groups: 3% in the SOC treatment group, compared to 7% in the buffer treatment group, and 6% in each of the 2 rhBMP-2/CMP treatment groups. The overall rate of infections in the current study (5%) is low and is comparable with the rate of infections in closed tibia fractures in the literature that ranges from 2 to 5%. Among all types of infections and infestations, only the incidence of osteomyelitis appeared to be statistically significant between the treatment groups (Fisher exact test, p-value=0.026), but not in pairwise comparisons with the other treatment groups. Osteomyelitis is considered to be a part of deep infections and was reported for 2 (3%) subjects in the buffer/CPM treatment group.

Delayed fracture union and nonunion
Delayed fracture union was defined as fracture not yet united 26 weeks after the injury and with no radiographic signs of progression toward union since the previous visit per the study visit schedule. The definition for nonunion was when 9 months had elapsed since the injury and the fracture site showed no visibly progressive signs of healing for a minimum of 3 months (no change in fracture callus). The incidence is similar between treatment groups: 5% in the SOC group versus 3% in each of the 3 injected groups.

Hardware Failure
HWF is comprised of bending breakage or loosening of the proximal and distal locking screws, not the IM nail itself. Device breakage, -component issue, -failure, or -malfunction in the RUS, occurred in 4 (6%) subjects in the SOC treatment group, 4 (7%) subjects in the buffer/CPM group, 8 (7%) subjects in the 1.0 mg/mL rhBMP-2/CPM treatment group, and 18 (14%) subjects in the 2.0 mg/mL rhBMP-2/CPM treatment group. The differences among the treatment groups were not statistically significant. .

Clinical Laboratory evaluation
Laboratory test results of clinical importance were noticed for 50 (81%) subjects in the SOC group, compared to 52 (87%) subjects in the buffer/CPM group, 99 (81%) subjects in the 1.0 mg/mL rhBMP-2/CPM group, and 108 (86%) subjects in the 2.0 mg/mL rhBMP-2/CPM group.

Immunogenicity Results: Overall, an authentic immune response developed in 3 (5%) subjects in the SOC group, 2 (3%) subjects in the buffer/CPM treatment group, 9 (7%) subjects in the 1.0 mg/mL treatment group, and 21 (17%) subjects in the 2.0 mg/mL treatment group. The highest incidence of an authentic response was at the 8-week visit. There were more subjects with authentic immune reactions in the 2.0 mg/mL rhBMP-2 group and it seemed the response lasted longer than in the other treatment groups. The incidence of an authentic response at the 9-month visit was not different among groups. No subjects developed neutralizing antibodies to BMP-2.

Other Results: The result of assessment of the feasibility of rhBMP-2/CPM indicate that at least 94% of the surgeons considered rhBMP-2/CPM preparation, ease of injection, ability to inject the entire volume, localize, and identify the rhBMP-2/CPM using fluoroscopy to be satisfactory.

CONCLUSIONS: There was no advantage of using rhBMP-2/CPM in addition to fracture fixation with locked, reamed IM nail for the treatment of closed tibia fracture. The 2 doses of rhBMP-2 (1.0 and 2.0 mg/mL) and the CPM were generally safe and well tolerated.