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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.: NCT00384852

PROTOCOL NO.: B1921005 (3100N7-212-WW)

PROTOCOL TITLE: A Phase 2, Multicenter, Double-blind, Randomized, Stratified, Controlled, Efficacy, Safety and Feasibility Study of Recombinant Human Bone Morphogenetic Protein-2 (rhBMP-2)/Calcium Phosphate Matrix (CPM) as an Adjuvant Therapy in Closed Fractures of the Humerus

Study Center(s): A total of 39 centers in 9 countries throughout the world took part in the study. A total of 6 centers in USA, 5 in Canada, 4 in Romania, 3 each in Australia and Mexico, and 1 each in Brazil, Finland and Sweden enrolled subjects.

Study Initiation Date and Primary Completion or Completion Dates:
10 January 2007 to 23 February 2010

Phase of Development: Phase 2

Study Objective(s):

Primary:

- To demonstrate that fracture union is accelerated in subjects with closed humeral fractures (proximal, shaft) treated with conservative therapy (considered the standard of care [SOC]) and a single dose of rhBMP-2/CPM (either 1.0 or 2.0 mg/mL) compared to subjects who are treated with SOC alone.

Secondary:

- To demonstrate the safety of administering rhBMP-2/CPM in subjects with closed humeral fractures, including key safety outcomes.

- To demonstrate feasibility by establishing a satisfactory method of administering rhBMP-2/CPM to implement in a Phase 3 efficacy trial for this clinical indication.

METHODS

Study Design: This was a Phase 2, multicenter, double-blind, randomized, stratified, Buffer/CPM and SOC controlled efficacy, safety, and feasibility study of rhBMP-2/CPM as an adjuvant therapy in subjects with closed fractures of the humerus treated by conservative therapy. All subjects received the SOC within 48 hours of their injury, which included fracture reduction (if necessary) and non-surgical fracture immobilization with a bracing device; and rehabilitation as prescribed by the investigator. Recombinant human bone morphogenetic protein-2/calcium phosphate matrix was administered once during the study. Regardless of treatment outcome, subjects were required to return for a total of 8 follow-up visits, beginning 4 weeks after injury through 1 year.

Number of Subjects (Planned and Analyzed): One hundred thirty-two subjects were planned to be enrolled in this study; 139 subjects were enrolled.

Diagnosis and Main Criteria for Inclusion: Subjects were skeletally mature, adult males or non-pregnant, non-nursing females, aged ≥18 years with closed proximal or diaphyseal humeral fracture (Orthopaedic Trauma Association classification 12A, 12B, or 12C) to be treated with conservative (non-operative) fracture immobilization therapy within 48 hours after injury (SOC).

Study Treatment: Subjects were randomly assigned (in a 1:2:2:1 ratio) to 1 of 4 treatment groups: SOC alone; 1.0 mg/mL rhBMP-2/CPM + SOC; 2.0 mg/mL rhBMP-2/CPM + SOC; and buffer/CPM + SOC. The injection occurred 5 to 10 days post injury and within 15 minutes of the study drug preparation. For either proximal humeral or humeral shaft fractures, the investigator was required to determine an optimal approach for delivering the study drug using anterior and/or lateral portals. Under fluoroscopic guidance, the fracture site was visualized and the delivery needle was placed via a percutaneous injection periosseously (around the fracture site) and/or intraosseously (within the fracture fragments) at the fracture site, depending on the fracture configuration. A total volume of 3 mL (±0.5 mL) of study drug was delivered.

Efficacy Evaluations: Evaluation of efficacy was based on radiographic evidence of fracture union, defined as visualization of callus bridging the fracture lines and/or obliteration (disappearance) of the fracture lines visualized on at least 3 of 4 aspects on orthogonal radiographic views, was assessed by an independent central evaluation committee. In order for the outcome to be considered a treatment success, radiographic union had to occur in the absence of any other procedure performed that would alter the process of fracture union. The study hypothesis was that the median time to fracture union in subjects with closed diaphyseal or proximal humeral fractures who received 3.0 mL of rhBMP-2/CPM (1.0 or 2.0 mg/mL) as an adjuvant treatment would be 4 weeks shorter than in subjects who received only the SOC.

Immunogenicity Evaluations: Serum samples were collected at baseline and at the visits scheduled for 6 and 26 weeks after injury to assess the prevalence and incidence of

anti-BMP-2 antibody formation using a validated enzyme-linked immunosorbent assays (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 to assess fracture-related complications, routine hematology and chemistry laboratory tests, and BMP-2 antibody testing.

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 site of administration.

Statistical Methods:
Efficacy: The primary efficacy endpoint was the time to radiographic union. Efficacy analyses were performed for the intent-to-treat (ITT) population. 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 (power 75%, α=0.1). The 2 pair wise comparisons of interest were 2.0 mg/mL versus SOC and 1.0 mg/mL versus SOC. These pair wise comparisons were performed sequentially. Primary analysis to determine acceleration of fracture union was performed when 108 subjects achieved treatment success in the ITT population.

Safety: Safety analyses were performed for the ITT population. Adverse events were tabulated and summarized by MedDRA system order class, preferred term, verbatim text, severity, region under study, and visit. All treatment groups were compared using a Chi-square test and Fisher's exact test for comparisons between 2 treatment groups. Adverse events in the region under study (RUS) were compared across treatment groups. Laboratory assays were analyzed by nonparametric methods (Wilcoxon signed rank and Kruskal-Wallis tests). Laboratory test values meeting prespecified criteria for potential clinical importance (PCI) at each time point were summarized with number and percentage and were tested with Fisher's exact test for comparisons between treatment groups. Chi-square test was used for testing the incidence of subjects with authentic BMP-2 antibody response across all groups and Fisher's exact test was used for comparisons between 2 treatment groups.

Others: The feasibility endpoint was analyzed using the injected population defined as only those subjects who were injected with rhBMP-2/CPM or buffer/CPM; any subject who received SOC alone was excluded. The feasibility of rhBMP-2 administration was summarized based on a dichotomous scale (satisfactory/unsatisfactory or yes/no) and tabulated by treatment group. The feasibility data were compared to a threshold value of a 75% satisfactory rating.

RESULTS

Subject Disposition and Demography: One hundred thirty-two subjects were planned to be enrolled. A total of 139 subjects were randomly assigned to SOC (23 subjects), buffer/CPM

(25 subjects), 1.0 mg/mL rhBMP-2/CPM (45 subjects), and 2.0 mg/mL rhBMP-2/CPM (46 subjects), including 7 subjects who discontinued before receiving the assigned treatment and whose treatment allocation was replaced. Disposition of subjects is presented in Table 1. A summary of the subject demography is presented in Table 2. Baseline fracture and injury characteristics were well balanced and therefore, are not deemed to have affected the safety outcomes.

Table 1 Summary of Subject Disposition

Subject Disposition	Standard of Care Control	Buffer/CPM Delayed	1.0 mg/mL rhBMP-2/CPM Delayed	2.0 mg/mL rhBMP-2/CPM Delayed	Total
Screened					153
Randomized	23	25	45	46	139
Discontinued and replaced subjects	1 (4)	2 (8)	2 (4)	2 (4)	7 (5)
Treated subjects	22 (96)	23 (92)	43 (96)	43 (93)	131 (94)
Randomized treatment not received	0	0	0	1 (2)	1 (<1)
Early conclusion	9 (39)	7 (28)	10 (22)	13 (28)	39 (28)
Subject request	4 (17)	3 (12)	3 (7)	4 (9)	14 (10)
Death	1 (4)	0	0	1 (2)	2 (1)
Lost to Follow-up	4 (17)	2 (8)	6 (13)	8 (17)	20 (14)
Noncompliance	0	1 (4)	0	0	1 (<1)
Other	0	1 (4)	1 (2)	0	2 (1)
Completed study	14 (61)	18 (72)	35 (78)	33 (72)	100 (72)

CPM=calcium phosphate matrix; rhBMP=recombinant human bone morphogenetic protein-2.
Treated: an enrolled subject who has received the randomized treatment assignment.

Table 2 Summary of Demographic Characteristics, Intent-to-Treat Population

Characteristic	Standard of Care Control n=22	Buffer/CPM Delayed n=23	1.0 mg/mL rhBMP-2/CPM Delayed n=43	2.0 mg/mL rhBMP-2/CPM Delayed n=44	Total n=132
Age (year)					
N	22	23	43	44	132
Mean	58.82	54.04	58.28	54.14	56.25
Standard deviation	15.57	20.36	18.45	18.54	18.31
Minimum	35.00	19.00	19.00	18.00	18.00
Maximum	88.00	95.00	89.00	87.00	95.00
Median	54.50	58.00	63.00	55.50	58.00
Age Category					
<65	15 (68)	16 (70)	25 (58)	28 (64)	84 (64)
≥65	7 (32)	7 (30)	18 (42)	16 (36)	48 (36)
Sex, n (%)					
Female	14 (64)	14 (61)	26 (60)	27 (61)	81 (61)
Male	8 (36)	9 (39)	17 (40)	17 (39)	51 (39)
Race, n (%)					
White	21 (95)	18 (78)	38 (88)	35 (80)	112 (85)
Black	0	1 (4)	1 (2)	1 (2)	3 (2)
Other	1 (5)	4 (17)	4 (9)	8 (18)	17 (13)
Height (cm)					
N	22	23	43	43	131
Mean	169.17	166.23	169.47	168.18	168.43
Standard deviation	7.79	7.82	10.93	10.34	9.73
Minimum	150.00	140.00	146.00	152.40	140.00
Maximum	188.00	181.00	195.60	193.00	195.60
Median	169.00	166.60	170.00	165.10	168.00
Missing	0	0	0	1	1
Weight (kg)					
N	22	23	43	43	131
Mean	77.69	79.30	77.65	78.50	78.22
Standard deviation	20.13	18.58	16.67	19.18	18.24
Minimum	52.20	45.00	50.80	49.90	45.00
Maximum	114.80	117.90	131.50	136.10	136.10
Median	72.85	77.10	75.00	78.00	76.00
Missing	0	0	0	1	1
Tobacco use, n (%)					
No	15 (68)	16 (70)	33 (77)	28 (64)	92 (70)
Yes	7 (32)	7 (30)	10 (23)	16 (36)	40 (30)

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

Efficacy Results: Time (in weeks) to radiographic fracture union and comparison of rhBMP-2 treatment groups and buffer/CPM versus SOC alone are provided for the ITT population in Table 3. Although the data were analyzed after 108 events, the results presented are for the complete data after all subjects had been followed until the end of the trial. The final analysis results are similar to the results at 108 events. The small improvement in median time to radiographic union when comparing 2.0 mg/mL rhBMP-2/CPM to SOC was not significant.

Table 3 Comparison of Time (Weeks) to Radiographic Fracture Union, Intent-to-Treat Population

	Standard of Care n=22	Buffer/CPM n=23	1.0 mg/mL rhBMP-2/CPM Delayed n=42	2.0 mg/mL rhBMP-2/CPM Delayed n=41
No. of subjects achieving union (n, %)	18 (81.8%)	21 (91.3%)	40 (95.2%)	37 (90.2%)
No. of censored subjects(n, %)[a]	4 (18.2%)	2 (8.7%)	2 (4.8%)	4 (9.8%)
Q1 time to union (90% CI)	5.4 (4.4, 6.1)	5.4 (4.6, 6.1)	5.7 (5.3, 6.7)	5.4 (3.7, 6.1)
Median time to union (90% CI)	7.1 (5.4, 9.4)	6.6 (5.6, 7.6)	7.2 (6.4, 8.0)	6.6 (5.7, 7.1)
Q3 time to union (90% CI)	9.4 (7.1, 18.1)	8.6 (6.6, 11.7)	8.9 (7.6,9.7)	8.7 (7.0,11.6)
Time to first union	2.9	3.9	2.9	2.7
Time to last union	18.1	15.4	18.0	27.3
Change in median time: Reference standard of care[b]		-0.6	0.1	-0.6
Log rank p-value: Reference standard of care		0.7308	0.9865	0.8000

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

Safety Results: Treatment-emergent AEs (TEAEs) reported by more than 10% of the subjects are presented in Table 4. The most common TEAEs were fracture displacement (35 subjects, 27%), hypocapnia (27 subjects, 20%), decreased carbon dioxide level (22 subjects, 17%), increased blood glucose level (19 subjects, 14%), increased blood alkaline phosphatase level (18 subjects, 14%), and peripheral edema (14 subjects, 11%). There were no significant differences among the treatment groups for these TEAEs.

Table 4 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=22	Buffer/CPM Delayed n=23	1.0 mg/mL rhBMP-2/ CPM Delayed n=43	2.0 mg/mL rhBMP-2/ CPM Delayed n=44	Total n=132
Any adverse event	**17 (77)**	**21 (91)**	**39 (91)**	**35 (80)**	**112 (85)**
Gastrointestinal disorders	6 (27)	7 (30)	5 (12)	5 (11)	23 (17)
Constipation	1 (5)	4 (17)	0	1 (2)	6 (5)
General disorders and administration site conditions	2 (9)	5 (22)	10 (23)	9 (20)	26 (20)
Edema peripheral	0	3 (13)	8 (19)	3 (7)	14 (11)
Infections and infestations	5 (23)	6 (26)	3 (7)	5 (11)	19 (14)
Nasopharyngitis	3 (14)	1 (4)	1 (2)	2 (5)	7 (5)
Injury, poisoning and procedural complications	9 (41)	10 (43)	24 (56)	21 (48)	64 (48)
Fall	1 (5)	3 (13)	1 (2)	3 (7)	8 (6)
Fracture [b]	2 (9)	1 (4)	6 (14)	7 (16)	16 (12)
Fracture displacement	6 (27)	6 (26)	12 (28)	11 (25)	35 (27)
Postoperative heterotopic calcification	0	1 (4)	4 (9)	8 (18)	13 (10)
Investigations	11 (50)	12 (52)	23 (53)	22 (50)	68 (52)
Alanine aminotransferase increased	2 (9)	3 (13)	4 (9)	2 (5)	11 (8)
Aspartate aminotransferase increased	3 (14)	3 (13)	3 (7)	3 (7)	12 (9)
Blood alkaline phosphatase increased	2 (9)	3 (13)	7 (16)	6 (14)	18 (14)
Blood bilirubin increased	3 (14)	0	0	0	3 (2)
Blood glucose increased	2 (9)	6 (26)	8 (19)	3 (7)	19 (14)
Carbon dioxide decreased	2 (9)	4 (17)	9 (21)	7 (16)	22 (17)
Hematocrit decreased	3 (14)	2 (9)	1 (2)	1 (2)	7 (5)
Hemoglobin decreased	3 (14)	2 (9)	2 (5)	6 (14)	13 (10)
Neutrophil count decreased	0	3 (13)	0	1 (2)	4 (3)
Metabolism and nutrition disorders	6 (27)	5 (22)	8 (19)	11 (25)	30 (23)
Hypocalcemia	3 (14)	0	0	2 (5)	5 (4)
Musculoskeletal and connective tissue disorders	8 (36)	13 (57)	16 (37)	17 (39)	54 (41)
Arthralgia	1 (5)	3 (13)	3 (7)	4 (9)	11 (8)
Musculoskeletal pain	3 (14)	3 (13)	2 (5)	6 (14)	14 (11)
Pain in extremity	0	3 (13)	5 (12)	4 (9)	12 (9)
Nervous system disorders	6 (27)	6 (26)	8 (19)	9 (20)	29 (22)
Headache	1 (5)	3 (13)	2 (5)	3 (7)	9 (7)
Psychiatric disorders	3 (14)	3 (13)	3 (7)	2 (5)	11 (8)
Renal and urinary disorders	1 (5)	3 (13)	1 (2)	0	5 (4)
Respiratory, thoracic and mediastinal disorders	4 (18)	7 (30)	9 (21)	14 (32)	34 (26)
Hypocapnia	2 (9)	5 (22)	8 (19)	12 (27)	27 (20)
Skin and subcutaneous tissue disorders	2 (9)	4 (17)	4 (9)	3 (7)	13 (10)
Vascular disorders	2 (9)	3 (13)	3 (7)	1 (2)	9 (7)

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 two 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 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."

The most common TEAEs in RUS were fracture displacement (35 subjects, 27%), fracture (16 subjects, 12%), musculoskeletal pain and postoperative heterotopic calcification (13 subjects, 10% each), and peripheral edema (12 subjects, 9%). The overall incidence of events was too low to draw conclusions about potential rhBMP-2/CPM relatedness.

Related TEAEs were reported for eight (19%) subjects in the 1.0 mg/mL rhBMP-2/CPM group and four (9%) subjects in the 2.0 mg/mL rhBMP-2/CPM group.

There was no significant difference between treatment groups in the incidence of safety outcomes occurring in the RUS of radial nerve palsy, delayed or non union, heterotopic bone formation, local edema, infection, pain, and adhesive capsulitis.

The incidence of serious AEs (SAEs) is presented in Table 5 by SOC and preferred term. The incidence of treatment-emergent SAEs was too low to draw final conclusions about causality.

There were 2 deaths during the study but they were not related to the treatment. One subject in the SOC group died of a cerebrovascular injury about 5 months after the fracture and another subject in the 2.0 mg/mL rhBMP-2/CPM treatment group died of a diabetic coma almost 1 year after the fracture.

Table 5 Number (%) of Subjects Reporting Serious Adverse Events

System Organ Class[a] Preferred Term	Standard of Care Control n=22	Buffer/ CPM Delayed n=23	1.0 mg/mL rhBMP-2/ CPM Delayed n=43	2.0 mg/mL rhBMP-2/ CPM Delayed n=44	Total n=132
Any serious adverse event	**7 (32)**	**4 (17)**	**5 (12)**	**6 (14)**	**22 (17)**
Cardiac disorders	0	0	0	2 (5)	2 (2)
Angina pectoris	0	0	0	1 (2)	1 (1)
Atrial fibrillation	0	0	0	1 (2)	1 (1)
Gastrointestinal disorders	3 (14)	1 (4)	0	0	4 (3)
Abdominal pain upper	0	1 (4)	0	0	1 (1)
Gastric ulcer	1 (5)	0	0	0	1 (1)
Gingival hyperpigmentation	1 (5)	0	0	0	1 (1)
Umbilical hernia, obstructive	1 (5)	0	0	0	1 (1)
General disorders and administration site conditions	0	1 (4)	0	0	1 (1)
Non-cardiac chest pain	0	1 (4)	0	0	1 (1)
Infections and infestations	0	2 (9)	0	1 (2)	3 (2)
Diverticulitis	0	1 (4)	0	0	1 (1)
Sepsis	0	1 (4)	0	0	1 (1)
Urinary tract infection	0	1 (4)	0	0	1 (1)
Wound infection staphylococcal	0	0	0	1 (2)	1 (1)
Injury, poisoning and procedural complications	2 (9)	2 (9)	1 (2)	2 (5)	7 (5)
Accidental overdose	0	0	1 (2)	0	1 (1)
Contusion	1 (5)	0	0	0	1 (1)
Foot fracture	0	1 (4)	0	0	1 (1)
Fracture displacement	1 (5)	1 (4)	0	2 (5)	4 (3)
Wound dehiscence	0	0	0	1 (2)	1 (1)
Metabolism and nutrition disorders	0	1 (4)	0	0	1 (1)
Diabetic ketoacidosis	0	1 (4)	0	0	1 (1)
Hyperglycemia	0	1 (4)	0	0	1 (1)
Musculoskeletal and connective tissue disorders	2 (9)	0	2 (5)	1 (2)	5 (4)
Arthralgia	1 (5)	0	0	1 (2)	2 (2)
Fracture delayed union	0	0	1 (2)	0	1 (1)
Fracture nonunion	1 (5)	0	1 (2)	0	2 (2)
Nervous system disorders	1 (5)	0	0	1 (2)	2 (2)
Cerebrovascular accident	1 (5)	0	0	0	1 (1)
Diabetic coma	0	0	0	1 (2)	1 (1)
Psychiatric disorders	0	0	0	1 (2)	1 (1)
Bipolar I disorder	0	0	0	1 (2)	1 (1)
Respiratory, thoracic and mediastinal disorders	0	1 (4)	1 (2)	0	2 (2)
Chronic obstructive pulmonary disease	0	0	1 (2)	0	1 (1)
Hypoxia	0	1 (4)	0	0	1 (1)
Pulmonary embolism	0	1 (4)	0	0	1 (1)
Respiratory failure	0	0	1 (2)	0	1 (1)
Skin and subcutaneous tissue disorders	1 (5)	0	0	0	1 (1)
Hyperkeratosis	1 (5)	0	0	0	1 (1)
Vascular disorders	1 (5)	1 (4)	1 (2)	0	3 (2)
Deep vein thrombosis	0	1 (4)	1 (2)	0	2 (2)
Thrombophlebitis	1 (5)	0	0	0	1 (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 two or more different adverse events within the higher level category.

Other Results: The results of the assessment for the feasibility of rhBMP-2/CPM indicated that at least 95% of the physicians considered rhBMP-2/CPM preparation, ease of injection, ability to inject the entire volume, and localize and identify the rhBMP-2/CPM using fluoroscopy to be satisfactory.

CONCLUSION(S): Injections of rhBMP-2/CPM were safe and generally well tolerated at the doses of 1.0 mg/mL and 2.0 mg/mL, and were feasible up to 3.0 mL. However, rhBMP-2/CPM did not improve times to fracture union. The evaluation of rhBMP-2/CPM in subjects with closed humeral fracture immobilized with a bracing device did not demonstrate a positive risk/benefit ratio to justify its use in this indication. The clinical development of rhBMP-2/CPM for the treatment of closed humeral fractures has been stopped.