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COMPOUND NUMBER: CP-533,536

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: Not applicable

NATIONAL CLINICAL TRIAL NO.: NCT00533377

PROTOCOL NO.: A3241010

PROTOCOL TITLE: A Randomized, Placebo-Controlled Study to Evaluate the Efficacy, Safety and Tolerability of CP-533,536 in Subjects with Closed Fracture of the Tibial Shaft

Study Centers: Australia (3), Bosnia and Herzegovina (1), Canada (7), Croatia (2), India (7), Japan (10), Russian Federation (2), South Africa (5), Spain (2), Turkey (5), United States (19)

Study Initiation Date and Primary Completion or Completion Dates: 09 Jan 2008 to 13 May 2010

Phase of Development: Phase 2

Study Objectives: Primary: (1) To assess the efficacy of a single dose of CP-533,536 (0.5 or 5 mg) in subjects with an operatively-treated closed tibial shaft fracture using radiographic measurements assessed by a central orthopedic reading panel, compared with PLGH (Poly D,L-lactide-co-glycolide) matrix treatment alone; (2) To determine the safety and tolerability of a single dose of CP-533,536 assessed by adverse event (AE) reporting and clinical laboratory measurements.

Secondary: (1) To assess the efficacy of a single dose of CP-533,536 (0.5 or 5 mg) in subjects with an operatively-treated closed tibial shaft fracture using radiographic measurements assessed by a central orthopedic reading panel, compared with standard of care treatment; (2) To assess the efficacy of a single dose of CP-533,536 (0.5 or 5 mg) in subjects with an operatively-treated closed tibial shaft fracture as assessed by the treating physician, compared with PLGH matrix alone; (3) To assess, based on the percentage of subjects healed at 14 weeks, the efficacy of a single dose of CP-533,536 (0.5 or 5 mg) in subjects with an operatively-treated closed tibial shaft fracture using radiographic measurements assessed by a central orthopedic reading panel, compared with PLGH matrix alone; (4) To assess the dose response characteristics of CP 533,536 using statistical modeling involving 4 doses of CP-533,536 (0.05, 0.16, 0.5, and 5 mg) and PLGH matrix alone if an extension utilizing two lower doses is implemented*; (5) To determine the impact of CP-533,536 (administered in a PLGH matrix) on the subject's ability to return to normal function, general health status, work productivity, and degree of pain at fracture site

compared with PLGH matrix alone and standard of care groups; (6) To determine the impact of CP-533,536 (administered in a PLGH matrix) on the proportion of subjects who required a secondary intervention to promote fracture healing compared with PLGH matrix alone and standard of care groups.

*The extension study was not implemented.

METHODS

Study Design: This was a 48-week, multi-center, single-dose, randomized, double-blind (except standard of care), parallel-group, standard of care and PLGH matrix (placebo)-controlled study of CP-533,536 in PLGH matrix administered to otherwise healthy subjects with closed fracture of the tibial shaft undergoing internal fixation using static reamed interlocked intramedullary (IM) nailing procedure. A total of 264 subjects were expected to be enrolled in this study.

Postoperatively, subjects were hospitalized for approximately 24 hours to monitor safety parameters and acquire pharmacokinetic (PK) samples.. Outpatient assessments continued at regular intervals for 48 weeks after treatment. After the hospitalization period, subjects returned for study visits on Week 1 and Week 8. The frequency of visits was every 2 weeks between Week 8 to Week 24 or until healed, whichever came first; thereafter, only those subjects who remained unhealed by Week 24 continued regular visits. Radiographs from each visit (except Week 48) were sent to the adjudication panel and reviewed by this panel on a regular basis for healing assessments.

An interim analysis was performed after approximately 180 subjects completed their Week 14 visit. Study personnel with direct oversight and conduct of the trial remained blinded to the interim analysis results.

All surgical procedures performed to promote fracture healing were proscribed for a period of 24 weeks after study treatment unless medically required. After Week 24, surgery or intervention to promote fracture healing may have been performed.

Number of Subjects (Planned and Analyzed): The planned sample size was 66 subjects per treatment group. Sample sizes analyzed ranged between 66 and 71 subjects per treatment group.

Diagnosis and Main Criteria for Inclusion: Males or females 17 years or older with confirmed closure of the tibial epiphyses, with a closed fracture of the tibial diaphysis undergoing treatment with static reamed locked IM nailing procedure and the absence of an associated compartment syndrome or vascular injury; subjects with fibular fractures may have been included. The static reamed locked IM nailing procedure must have been completed between 0 to 14 days post-injury. Subjects who had previous fractures of the same tibia that may have impacted the nailing procedure or impaired visibility of current fracture, or a history of osteomyelitis were excluded, as were subjects with any other clinically significant injuries, which potentially significantly impaired weight bearing of the affected limb. Any other planned invasive or noninvasive interventions intended to promote

bone healing of the tibial fracture under study were not allowed in the first 24 weeks after treatment.

Study Treatment: Study medication in this trial was administered only once during the primary surgical repair of the tibial fracture. The investigator injected study drug percutaneously (under fluoroscopy) into the fracture site after completion of the IM nailing procedure. Subjects in the standard of care group received no injection.

Efficacy Evaluations: The primary assessments were orthopedic examinations and radiographs of the fracture. Anteroposterior and lateral radiographs of the treated limb were taken prior to surgery, intraoperatively to document needle placement, within 24 hours after surgery, at 1, 8, 10, 12, 14, 16, 18, 20, 22, 24, 28, 32, 36, 40, 44 and 48 weeks after surgery (or until healing was determined by the adjudication committee, whichever came first), and at the After Healing Visit. Radiographs (other than Week 48) were sent to a central adjudication center for processing, formatting and independent assessment by a blinded orthopedic panel consisting of 5 surgeons. The panel independently assessed fracture healing using a web-based adjudication system. Regular meetings of the panel were conducted to reach consensus on fracture healing in all subjects. The consensus decision of the committee was considered final.

The following subject-reported outcomes were assessed: The American Academy of Orthopedic Surgeons (AAOS) Lower Limb Instrument, The EuroQol-5 Dimension (EQ-5D) health questionnaire, the Short-Form 12 (SF 12) general health questionnaire, and the Work Productivity and Activity Impairment (WPAI) Questionnaire.

Safety Evaluations: The safety and tolerability of CP-533,536 were assessed after dosing and at subsequent study visits by regular clinical monitoring and included physical and orthopedic examination, safety laboratory assessments (chemistry, hematology, urinalysis), 12-lead electrocardiograms (ECGs), supine vital sign measurements (blood pressure [BP] and heart rate [HR]), and AE monitoring. Female subjects of childbearing potential were tested for serum beta human chorionic gonadotropin (β-hCG) at screening, and urine β-hCG throughout the study.

Statistical Methods: The null hypothesis was of the no-effect form, meaning that the population parameters in question were equal in the control and test groups versus 2-sided alternative hypotheses of inequality between treatment and control groups. The results were considered to be clinically successful only if, in addition to a statistically significant difference based on the log-rank test, the lower bound for the 80% confidence interval (CI) for the difference in median healing times between each of the CP-533,536 doses plus PLGH matrix treatment groups and the PLGH matrix (placebo) treatment group was less than the value that corresponded to an approximately 20% reduction in the median healing time in the PLGH matrix (Placebo) treatment group. The Kaplan-Meier method was used to estimate the distribution of time to fracture healing for each of the treatment groups, with estimates of the median, first and third quartiles provided. Differences in the survival distributions between treatment groups were assessed using a two-sided unstratified log rank test with $\alpha = 0.05$ as the level of significance. The median time to event, as well as the 25th and 75th percentiles, was presented with 95% confidence limits. The mean time to healing was also

provided. Two-sided 80% CIs for the difference in median time to event for each "CP-533,536 plus PLGH Matrix Group" and the "PLGH Matrix Alone Group" were calculated using the method of Su and Wei. The primary analyses were repeated in the per protocol (PP) set, which excluded subjects from the full analysis set (FAS) who missed 1 or more windowed visit just preceding a healing assessment.

Additionally, as a secondary evaluation based on the primary endpoint, the two-sided 80% CI for the difference in median time to event for the PLGH matrix alone group versus the standard of care group should not have included a 20% difference.

Secondary analyses were performed for the FAS only. Time to fracture healing based on radiographs plus clinical information and time to fracture healing based on radiographs as assessed by the adjudication panel was analyzed using the methodology described above for the primary analysis (log rank tests, 80% CI for differences in median healing times, Kaplan Meier survival curves).

Continuous endpoints were summarized using descriptive statistics, which included: number of subjects (N), mean, median, standard deviation, minimum, and maximum. Outcomes measures were assessed using descriptive statistics.

Safety parameters were presented in the sponsor's standard format.

RESULTS

Subject Disposition and Demography: Table 1 summarizes subject disposition in this study. Of the 266 subjects treated, 227 completed the study. A total of 39 subjects discontinued the study, 1 of whom discontinued due to an AE judged unrelated to the study drug. Two subjects died for reasons unrelated to the study drug.

Table 1. Subject Disposition

	CP-533,536 0.5 mg	CP-533,536 5 mg	Standard of Care	Placebo
Number of subjects screened 288				
Number of subjects assigned to study treatment	66	67	71	70
Treated	64	65	69	68
Completed, n (%)[a]	55 (83.3)	57 (85.1)	60 (84.5)	55 (78.6)
Discontinued, n (%)[a]	9 (13.6)	8 (11.9)	9 (12.7)	13 (18.6)
Discontinuations, n (%)[b]				
Relation to study drug not defined	8 (12.5)	8 (12.3)	9 (13.0)	11 (16.2)
Lost to follow-up	5 (7.8)	8 (12.3)	7 (10.1)	6 (8.8)
Protocol violation	1 (1.6)	0	0	0
Subject no longer willing to participate in study	2 (3.1)	0	1 (1.4)	5 (7.4)
Withdrawn due to pregnancy	0	0	1 (1.4)	0
Not related to study drug				
Adverse event	0	0	0	1 (1.5)
Subject died	1 (1.6)	0	0	1 (1.5)

Table 1. Subject Disposition

	CP-533,536 0.5 mg	CP-533,536 5 mg	Standard of Care	Placebo

Discontinuations occurring outside the lag period were attributed to the last study treatment received.
Abbreviations: n = number of subjects, mg = milligrams
[a]Percentages calculated using number of subjects assigned to study treatment as the denominator.
[b]Percentages calculated using number of subjects actually treated as the denominator.

More males than females were enrolled in each of the dose groups. Most subjects were White or Asian, between 18 and 44 years of age, with mean ages for each dose group ranging between 35.6 and 41.3 years.

Efficacy Results: The primary efficacy endpoint was the time to fracture healing during the first 24 weeks after treatment assessed by the orthopedic panel using radiographic measurements from the FAS. There were no statistically significant differences between the active drug, standard of care, and placebo; thus, proof of concept was not achieved for the primary endpoint. In addition, there were no clear differences between placebo and standard of care. Similar results were seen in the PP set.

Secondary evaluations and patient-reported outcomes also revealed no statistically significant differences among treatment groups.

Safety Results: All AEs discussed in this report were treatment-emergent. The most frequently reported all causality AEs are presented in Table 2.

Table 2. Frequently Reported AEs by Maximum Severity in ≥2 Subjects in any Treatment Group (All-Causality)

	CP-533,536 0.5 mg N = 64				CP-533,536 5 mg N = 65				Standard of Care N = 69				Placebo N = 68			
MedDRA Preferred Term	**n (%)**	**M**	**Mo**	**Sev**	**n (%)**	**M**	**Mo**	**Sev**	**n (%)**	**M**	**Mo**	**Sev**	**n (%)**	**M**	**Mo**	**Sev**
Procedural pain	3 (4.7)	1	2	0	2 (3.1)	1	1	0	5 (7.2)	4	1	0	2 (2.9)	1	1	0
Edema peripheral	3 (4.7)	2	0	1	2 (3.1)	2	0	0	4 (5.8)	3	1	0	2 (2.9)	2	0	0
Pain in extremity	3 (4.7)	1	2	0	1 (1.5)	1	0	0	2 (2.9)	1	1	0	3 (4.4)	2	1	0
Pyrexia	2 (3.1)	1	1	0	2 (3.1)	1	1	0	3 (4.3)	3	0	0	2 (2.9)	0	2	0
Nasopharyngitis	2 (3.1)	1	1	0	2 (3.1)	2	0	0	1 (1.4)	1	0	0	2 (2.9)	2	0	0
Arthralgia	1 (1.6)	0	1	0	0	0	0	0	2 (2.9)	1	1	0	3 (4.4)	3	0	0
Hypoesthesia	1 (1.6)	1	0	0	0	0	0	0	4 (5.8)	4	0	0	0	0	0	0
Constipation	0	0	0	0	2 (3.1)	1	0	1	2 (2.9)	1	1	0	0	0	0	0
Fall	0	0	0	0	1 (1.5)	0	0	1	3 (4.3)	3	0	0	0	0	0	0
Fracture	3 (4.7)	1	2	0	0	0	0	0	1 (1.4)	1	0	0	0	0	0	0
Headache	0	0	0	0	0	0	0	0	2 (2.9)	2	0	0	2 (2.9)	1	0	1
Post procedural discharge	2 (3.1)	2	0	0	0	0	0	0	2 (2.9)	2	0	0	0	0	0	0
Influenza	0	0	0	0	2 (3.1)	2	0	0	1 (1.4)	0	1	0	0	0	0	0
Insomnia	1 (1.6)	1	0	0	0	0	0	0	0	0	0	0	2 (2.9)	2	0	0
Musculoskeletal pain	0	0	0	0	1 (1.5)	1	0	0	2 (2.9)	2	0	0	0	0	0	0
Nausea	2 (3.1)	2	0	0	1 (1.5)	1	0	0	1 (1.4)	1	0	0	1 (1.5)	1	0	0
Pruritus	1 (1.6)	1	0	0	0	0	0	0	2 (2.9)	1	1	0	0	0	0	0
Incision site infection	2 (3.1)	2	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Localized infection	0	0	0	0	2 (3.1)	2	0	0	0	0	0	0	0	0	0	0
Pain	0	0	0	0	0	0	0	0	0	0	0	0	2 (2.9)	0	1	1
Rash	0	0	0	0	0	0	0	0	2 (2.9)	2	0	0	0	0	0	0
Toothache	0	0	0	0	0	0	0	0	2 (2.9)	2	0	0	0	0	0	0

If the same subject in a given treatment had more than 1 occurrence in the same preferred term event category, only the most severe occurrence was taken. Subjects were counted only once per treatment in each row. For the TESS algorithm any missing severities were imputed as severe unless the subject experienced another occurrence of the same event in a given treatment for which severity was recorded. In this case, the reported severity was summarized. Missing baseline severities were imputed as mild. This table includes data up to 9999 days after last dose of study drug. Percentages for gender-specific events use the corresponding gender count as a denominator. MedDRA (v13.0) coding dictionary applied.

Abbreviations: AE = adverse event, MedDRA = Medical Dictionary for Regulatory Activities, TESS = treatment-emergent signs and symptoms, M = mild, Mo = moderate, Sev = severe, N = number of subjects in each treatment group, n = number of subjects in each category of AE, v = version, mg = milligrams

Two subjects discontinued the study due to AEs judged unrelated to the study drug (vascular injury and drug exposure during pregnancy). There were no temporary discontinuations or dose reductions in this study.

Two subjects died as a result of serious adverse events (SAEs) that occurred post-therapy and that were judged unrelated to the study treatments. One 84-year-old Asian female from India who received 0.5 mg CP-533,536, and one 68-year-old Asian male from Japan who received placebo (Table 3).

Table 3. Deaths (FAS)

Treatment Group	Sex/Age (years)	Serious Adverse Event MedDRA Preferred Term	Study Start/Stop Day	Causality; Subject Action	Action taken (drug level)
CP-533,536 0.5 mg	Female/84	Respiratory failure	[>60]	Respiratory failure	Post-therapy
Placebo	Male/68	Multi-organ failure	[>216]	Multi-organ failure, acute myocardial infarction	Post-therapy

[] Value in brackets was imputed from incomplete dates and times.
MedDRA (v13.0) coding dictionary applied.
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, No. = number, FAS = full analysis set, v = version

A total of 22 subjects experienced SAEs during this study, none of which related to treatment (Table 4).

Table 4. Serious Adverse Events (FAS)

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Treatment Group	Sex/Age (years)	Serious Adverse Event MedDRA Preferred Term	Severity	Study Start/Stop Day	Causality; Subject Action	Outcome
CP-533,536						
0.5 mg	Male/20	Hypoxia	Severe	2/ 5	Other illness-probable aspiration pneumonitis versus community acquired pneumonia; bibasilar pulmonary infiltrates; treatment given	Resolved
	Female/84	Respiratory failure[a]	Severe	60/[>60]	Other-reason not known; no action	Still present
		Deep vein thrombosis	Moderate	19/[>60]	Other-reason not known; treatment given	Still present
	Female/66	Implant site erythema (at entry point of intramedullary nail site)	Mild	3/13	Other-the reason for erythema could be related to surgical procedure	Resolved
		Erythema (at fracture site)	Mild	3/13	Other-the erythema could have been related to the surgical procedure	Resolved
	Male/34	Infection	Severe	8/41	Disease under study; treatment given, hospitalization	Resolved
		Peripheral embolism (suspected microembolism of left leg)	Mild	8/20	Disease under study; treatment given	Resolved
	Male/21	Pulmonary embolism	Severe	8/56	Other illness-bronchitis; treatment given	Resolved
5 mg	Male/30	Fall	Severe	79/79	Other-tripped over protruding nail on deck at residence; hospitalized for wrist fracture	Resolved
		Wrist fracture	Severe	79/[>337]	Other – fall; patient hospitalized and underwent open reduction internal fixation left wrist fracture	Still present
	Female/23	Pain in extremity (in right leg)	Mild	366/375	Other-broken screw; removal of implant	Resolved
	Female/33	Subcutaneous abscess (on right lower limb)	Mild	42/70	Other-osteitis; needs formal incision, drainage and debridement of the abscess	Resolved
	Male/59	Blister infected	Moderate	8/13	Disease under study; treatment given	Resolved

[a]Subject died.
MedDRA (v13.0) coding dictionary applied.
[] Value in brackets was imputed from incomplete dates and times.
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, v = version, mg = milligrams

Table 4. Serious Adverse Events

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Treatment Group	Sex/Age (years)	Serious Adverse Event MedDRA Preferred Term	Severity	Study Start/Stop Day	Causality; Subject Action	Outcome
5 mg	Male/23	Compartment syndrome	Severe	2/2	Disease under study; treatment given	Resolved
		Skin disorder	Moderate	2/16	Disease under study; treatment given	Resolved
	Male/21	Device connection issue (loosening of tibial nail screw)	Severe	99/100	Disease under study; treatment given (screw removal)	Resolved
		Medical device connection issue (intramedullary nail instability)	Moderate	185/186	Disease under study; treatment given (intramedullary nail removal)	Resolved
Standard of Care	Male/39	Cellulitis	Moderate	173/183	Other illness-staphylococcus epidermidis; treatment given	Resolved
		Neuropathy peripheral	Severe	166/[>338]	Other-nerve injury from fall; treatment given	Still present
	Male/71	Device failure (failed fixation of the left proximal tibial fracture)	Moderate	18/18	Other-fall on 10-14-2008; treatment given	Resolved
		Fall	Mild	18/18	Other illness – Parkinsons	Resolved
	Male/69	Venous thrombosis limb (phlebothrombosis of left lower leg)	Moderate	81/103	Other-immobilization/surgery; treatment given	Resolved
	Male/69	Hemorrhagic anemia	Moderate	6/16	Disease under study; treatment given	Resolved
		Cardiac failure	Mild	6/16	Other – unknown; treatment given	Resolved
		Pneumonia	Mild	5/16	Other – unknown; treatment given	Resolved
		Folate deficiency	Mild	6/16	Other – unknown; treatment given	Resolved
		Vitamin B12 deficiency	Mild	6/16	Other – unknown; treatment given	Resolved
Placebo	Male/29	Major depression	Severe	228/255	Other illness-depression; treatment given	Resolved
		Substance abuse (polysubstance abuse)	Severe	228/255	Other illness-substance abuse; treatment given	Resolved
	Male/22	Vascular injury	Severe	1/29	Other-vascular injury with compartment syndrome; treatment given (fasciotomy, ct angiography embolectomy, discontinue study)	Resolved

MedDRA (v13.0) coding dictionary applied.
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Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, CT = computed tomography, v = version, mg = milligrams

Table 4. Serious Adverse Events

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Treatment Group	Sex/Age (years)	Serious Adverse Event MedDRA Preferred Term	Severity	Study Start/Stop Day	Causality; Subject Action	Outcome
Placebo	Male/29	Pulmonary oedema	Moderate	2/3	Other-post tibial/fibula fracture surgery, subject was coughing. Lung infection suspected, in connection with pulmonary oedema and hypoxia; treatment given (spiral CT chest)	Resolved
	Female/30	Impaired healing (abnormal healing of left lower leg)	Moderate	99/335	Disease under study; treatment given (intramedullary nail dynamization)	Resolved
		Hematoma infection (hematoma inflammation on left lower leg)	Moderate	31/42	Disease under study; treatment given (surgical debridement of hematoma)	Resolved
	Male/68	Acute myocardial infarction	Severe	214/[>216]	Other illness-causality is due to diabetes mellitus, hypertension or other factors; treatment given	Still present
		Ventricular fibrillation	Severe	214/[>216]	Other illness-due to acute myocardial infarction; treatment given	Still present
		Multi-organ failure	Severe	214/[>216]	Other illness-due to acute myocardial infarction intractable ventricular fibrillation hypoxicencephalopathy; treatment given	Still present
		Hypoxic encephalopathy	Severe	214/[>216]	Other illness-due to intractable ventricular fibrillation; treatment given	Still present
	Male/53	Device failure	Moderate	27/154	Disease under study; treatment given (treatment given,planned open reduction internal fixation)	Resolved
	Male/22	Hemoptysis	Moderate	3/6	Other-thorax trauma, lung contusion: no action	Resolved

MedDRA (v13.0) coding dictionary applied.
[] Value in brackets was imputed from incomplete dates and times.
Abbreviations: MedDRA = Medical Dictionary for Regulatory Activities, v = version, mg = milligrams, CT = computed tomography

Overall, fewer than 10% of subjects experienced treatment-related AEs in any treatment group, with a slightly higher proportion of AEs occurring in the CP-533,536 and standard of care treatment groups. No severe AEs were judged by the investigator to be treatment-related.

AEs attributed to CP-533,536 0.5 mg were single instances of pyrexia, cellulitis, foot deformity, acne, hypertension, and nausea. Pyrexia, cellulitis, acne, and nausea resolved during the study. AEs attributed to CP-533,536 5 mg were single instances of limb injury (left toe split open), alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, and decreased appetite. ALT increased, AST increased, and decreased appetite resolved during the study. AEs attributed to standard of care were 2 instances of procedural pain, and single instances each of peripheral edema, myalgia, areflexia, and hypertensive crisis. The single AE attributed to placebo was cellulitis. Foot deformity, hypertension, limb injury, procedural pain, peripheral edema, myalgia, areflexia, hypertensive crisis, and cellulitis were still present at the end of the study, and their causality was missing from the database; thus, the causality of these AEs was attributed to the study treatment per Sponsor data reporting standards.

Conclusions:

- There were no statistically significant differences between 0.5 mg CP-533,536, 5 mg CP-533,536, standard of care, and placebo.

- CP-533,536 appeared to be safe and well tolerated at the doses administered in this study.