Protocol
PTH(1-34) and Pelvic Fracture Healing - a Randomized Controlled Trial-
Version 6- June 21, 2019
Identifiers: NCT02972424 Unique Protocol ID: 2015-330
IND 126129

1. General Information

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Protocol Summary:

This is a prospective randomized, double-blinded, placebo-controlled, phase 2, three-month study of the efficacy of TPTD in postmenopausal women and men ≥ 65 years of age with acute fractures of the pelvis. We will extend this study with 9 months of open label TPTD to determine if any potential differences between the placebo and TPTD groups during the 3 months of treatment are evident and persist over time, even in patients who use TPTD after the three month placebo controlled intervention.

We will include men or women with single or multiple rami fractures and a presence of absence of sacral fracture. We will randomize 100 patients 1:1 in a blinded fashion to receive either 20mcg of TPTD subcutaneously (SC) every day or identically appearing placebo SC for 12 weeks. All patients will have ideal medical care for comorbidities, pain management and progressive mobilization. A routine clinical protocol will be followed to quickly normalize 25-hydroxyvitamin D (goal >20 ng per milliliter; the current IOM guideline 201035) before starting treatment. All patients will receive a loading dose of vitamin D2 (at a dose of 50,000 IU given orally). After the loading dose, daily supplementation with 1000 IU vitamin D will be used for the duration of the study. This will allow for patients to be recruited and to begin the trial of TPTD or placebo within 2 weeks of the fracture with improved 25(OH)D levels. Calcium intake will be assessed and dietary suggestions or supplementation will be used to bring total intake to approximately 1000 mg a day, slightly lower than the recommended calcium intake for women over age 50 (in order to prevent hypercalcemia).

Our primary outcome is radiographic evidence of fracture healing at the 12-week endpoint. At 4, 8 and 12 weeks after initiating TPTD or TPTD placebo, all patients will get follow-up pelvic radiographs, although these radiographs will stop when healing occurs. If the radiologist notes cortical bridging on the monthly x-ray, or at 3 months a confirmatory limited low dose Focus CT at the fracture site(s) will be performed to assess the degree of bridging. Cortical bridging will be quantified with bridging of 3 or 4 cortices as "healing", 1 or 2 cortices as "partial healing", and 0 cortices as "minimal/no healing" by two independent radiologists and adjudication by a third. If there are multifocal fractures, cortical bridging at each site will be evaluated and an adjudicated score representing the state of healing (0 to 4) will be recorded. Secondary analysis will examine treatment group differences in the change in follow-up pelvic fracture healing scores over the repeated monthly assessments during the 3 month placebo-controlled phase.

A secondary outcome is pain and narcotic use. The numeric rating scale (NRS) will be administered by research staff that is blinded to treatment group. We will also quantify use of narcotics and other adjunct medications for pain by recording their reported use and also asking for narcotic bottles to be brought in at each visit and performing a pill count. The NRS and recording of pain medications will be done at baseline, 4, 8 and 12 week visits and at the 6, 9 and 12 month visits.

Another secondary outcome is lower extremity physical function at 3 months and again from 3-12 months. Physical performance tests will be administered by research staff that is blinded to treatment group. The lower extremity physical function tests, tests include normal walking speed over 4 meters (with or without an assistive device), repeated chair stands (stand up from a chair with their arms folded across their chest), and balance (ability to maintain balance for 10 seconds in each of 3 positions: side-by-side, semi-tandem, and tandem foot positions). In addition, the Timed Up and Go test will be completed by each subject. Each subject will also complete the survey of ADLs and the SF-36.

The primary outcome analysis is an ITT analysis of the categorization of the level of cortical bridging see on focus CT at 3-months. The operational definition of cortical bridging is a five-level ordinal scale from “not healed” to “healed” (cf. protocol) adjudicated by the radiologists and clinicians, with two qualifications: 1) if endpoint assessment is missing because of a drop-out or loss-to-follow subsequent to an AE or SAE, the endpoint will be coded as “not healed”; 2) if the endpoint is missing for any other reason, the endpoint will be coded as the last available coding of the focus CT assessment. The treatment difference in cortical bridging will be evaluated by a 2x5 chi-square (group x score) with a trend test (Jonckheere-Terpstra) for the ordinal

level of bridging to see whether the TPTD treated participants “trend” to have a greater proportion of higher bridging scores than the placebo group.

Secondary analysis of the treatment group differences in the change in fracture healing scores across the 3-months of the placebo-controlled phase will use a generalized estimating equation for longitudinal repeated measures assuming a Poisson distribution with observation-level weighting from a logistic regression analysis of the missingness pattern following the approach used by Fitzmaurice, Lair and Ware (2011). The outcome will be coded as described for the primary outcome ITT analysis. Missing covariate values will be filled using the fully conditional specification multiple imputation method to impute a monotonically missing data pattern: outcomes will not be imputed. Continuous covariates will use the predictive mean matching method while classification covariates will use a logistic regression method.

For the secondary outcome of pain, we will use a between-groups linear mixed model for repeated measures (LMMrm) to estimate the between-group difference in the mean within-subject change from baseline to the end of the placebo controlled trial (0-3 months) and again to explore change from 3 to 12 months in the open label extension. Narcotic and non-narcotic pain medication use will enter the model as time-dependent covariates. Separately, treatment group differences in the cumulative narcotic and non-narcotic drug exposure in the 3-month placebo-controlled phase will also be estimated with linear mixed model for repeated measures. This analysis addresses the two questions, “Do patients treated with TPTD show more rapid reduction in reported pain level than those not so treated? If so, when?”

For the secondary outcome of lower limb physical function, we will use a between-groups linear mixed model for repeated measures (LMMrm) model for the analysis to estimate the difference in within-subject change from 0 to 3 months in the CSPP score in the two groups. A secondary analysis for this aim will explore the changes in physical function from 3 to 12 months in the two groups.

If TPTD can improve fracture healing, this study will have an impact on the treatment of persons with pelvic fracture who are not surgical candidates and often face severe pain, chronic immobility, and loss of function in the elderly. A positive finding of accelerated healing of pelvic fractures would also encourage study of TPTD for treatment of other osteoporotic fractures.

2. Trial Objectives and Purpose:

By 2030 over 25% of the entire US population will be older than 65 years of age. Pelvic fracture rates are higher in women[1] Over 90% of pelvic fractures in patients >60 years are defined as osteoporosis related fractures.[2] In a recent study in Germany, the rate of all first pelvic fractures in persons over 60 was 22.4 [95% CI 22.0–22.9] per 10,000 person-years.[3] The incidence rate increases dramatically with age, from 5.4 and 3.8 per 10,000 person-years in women and men aged 65 to 69 years to 93.5 and 44.5 per 10,000 person-years in women and men aged 90 years and older, respectively.[4] This is in agreement with studies in the US and Finland, also showing an increase in incidence of pelvic fractures with age.[2,5] Pelvic fractures are most often a result of low-energy trauma, such as a fall from standing height. Pelvic fractures are the most relevant for this proposed randomized placebo controlled study. This fracture is accompanied by severe pain, chronic immobility and loss of function and independence in the elderly.[6] The current treatment strategy of pelvic fractures includes pain management, patient mobilization, and the prevention of complications associated with comorbid conditions. In a review of six studies with over 500 patients,[7] the mean length of hospital stay was 13.4 days and the average 1-year mortality was 16.3%. Mortality rates in 1300 pelvic fracture patients were still elevated at 3 years.[1] Pelvic fractures are associated with slow healing and a delayed return to full function and normal activity.[8] Pelvic fractures consume substantial healthcare resources, and based on administrative claims data, they are one of the most costly osteoporosis related fractures.[9] Un-healed fractures, occurring in one-third of pelvic fracture patients at 3 months,[8] can cause continued pain and impact mobility. With aging of the population, and expected concomitant increase in the incidence of pelvic fractures, there is a pressing need to find effective treatments that will accelerate healing. There are strong preclinical data[10-13] as well as clinical evidence that administration of parathyroid hormone (PTH) peptides may improve bone union, hasten fracture healing and improve physical function.[8,11,13-15] In one nonrandomized, un-blinded study, 100% of pelvic

fracture patients given 1-84PTH were healed within 12 weeks compared to 68% of the controls.[8] However, there is not sufficient evidence at this time to recommend routine use of PTH peptides for fracture healing. Pelvic fractures are ideal to study for the impact of Teriparatide (TPTD) on rate of fracture healing because there are no surgical repairs for the vast majority of the fractures. Prior studies of TPTD on wrist fracture healing were limited and confounded by the increased prevalence of surgical fixation to treat these fractures.[14] Strong evidence of pelvic fracture healing that may result from this study may not only have an impact on pelvic fractures but perhaps may indicate a potential use for other fractures as well.

In our proposed randomized, double blind, placebo controlled clinical trial in patients >65 years of age with acute pelvic fracture, we plan to evaluate whether treatment with daily subcutaneous TPTD 20 mcg/day compared with placebo, in addition to standard treatment (pain management, bed rest and prevention of complications from comorbid conditions), is effective in accelerating fracture healing in women and men compared to standard treatment alone. We hypothesize that development of a successful adjunctive therapy (TPTD) will accelerate radiographic evidence of fracture healing and speed functional recovery. If this hypothesis holds true, it would lead to a change in clinical practice and an improved quality of care for pelvic fracture patients. Evidence of an impact on the healing of pelvic fractures may also extend to a potential to improve healing of other osteoporosis-related fractures. In the planned trial we will recruit women and men with acute pelvic fractures and address 3 specific aims over 3 months of treatment in a placebo controlled double blind study to determine if **TPTD** in addition to standard care ***versus placebo*** and standard care:
1. Results in ***earlier evidence of cortical bridging*** on routine radiographs followed by confirmatory Focus CT, a novel method to reduce radiation exposure from CT scans (primary outcome).
2. Leads to ***a faster reduction in pain*** as assessed by both the Numeric Rating Scale and a reduction in the use of narcotics (secondary outcome).
3. Leads more to a more rapidly ***improved functional outcome*** using a short physical performance battery to assess lower extremity function (secondary outcome).

Although our primary analysis will be based on data from 0 to 3 months, whether the benefit of TPTD on fracture healing wanes over time is unclear,[16] making a longer follow-up important to extend our knowledge on the persistence of early TPTD effect on these outcomes. Therefore, we will extend this study with 9 months of open label TPTD to determine if any potential differences between the placebo and TPTD groups during the 3 months of treatment are evident and persist over time, even in patients who use TPTD after the three month placebo controlled intervention.

If TPTD can improve fracture healing, this study will have an impact on the treatment of persons with pelvic fracture who are not surgical candidates and often face severe pain, chronic immobility, and loss of function in the elderly. A positive finding of accelerated healing of pelvic fractures would also encourage study of TPTD for treatment of other osteoporotic fractures.

3. Background:

The economic and clinical toll of osteoporosis related fractures is well known.[17] Most fractures among the aging population are at least in part related to osteoporosis and the costs for acute health care alone top $15 billion annually. Pelvic fractures are among the most costly osteoporosis related fractures due to loss of function, long hospitalizations and rehabilitation and the difficulty in managing these fractures.[18,19] Pelvic fractures can serve as a model of fracture healing for other osteoporosis related fractures. Success in this trial may also help encourage patients and doctors to initiate treatment soon after a fracture. This is important because subsequent fractures occur with greatest frequency shortly after the first fracture.[20] The drug, rhPTH(1-34), referred to in this application as Teriparatide (TPTD), is currently marketed as a treatment for osteoporosis in men and women at high risk of fracture. Elderly patients with non-traumatic pelvic fracture have osteoporosis and are at high risk for future fracture, thus are eligible for treatment with TPTD. TPTD stimulates bone formation and remodeling with formation of new bone tissue, improved skeletal architecture, increased bone mass (i.e. a true increase in the amount of bone tissue), and potentially by periosteal bone formation, an increase in the diameter of some bones in the skeleton.[21-24] A large body of evidence in preclinical models supports the concept that TPTD can improve fracture healing.[10-13] In addition, daily subcutaneous injection of TPTD for bone union using local bone grafting after instrumented lumbar posterolateral fusion in women with postmenopausal osteoporosis was more effective than oral administration of bisphosphonate in an observational study.[15] Recently, an acceleration of fracture healing with TPTD (20 mcg per day) was reported

in a randomized controlled trial of 102 postmenopausal women who had sustained a distal radial fracture.[14] The authors concluded that their result should be interpreted with caution and noted that there was no further improvement with the 40 mcg dose. This provides rationale for our using a dose of 20 mcg TPTD per day. A recent study[8] reported the successful use of PTH 1-84 to enhance the healing of fractures of the pubic ramus in 65 patients, based on x-ray and CT images. This study was not randomized or blinded and is therefore subject to bias, particularly since patients in the PTH 1-84 treatment group were treated at a single center, and patients from both this center and another center served as controls (no PTH 1-84 treatment). In that study, 100 mcg of PTH 1-84 (equivalent to about 40 mg TPTD) resulted in fracture healing at a mean of 7.8 weeks, and 100% of the treated group had healed at 8 weeks following PTH1-84 administration, significantly faster than the control group (9% healed at 8 weeks and 68% at 12 weeks). Results of that study need to be confirmed for several reasons. First, a randomized, controlled, blinded study is required. Second, there may be some difference between 1-84PTH and 1-34PTH, as illustrated in a small study comparing the effects of these two peptides on cortical porosity assessed by high resolution pQCT.[25] However, it does add to the growing clinical evidence that PTH peptides may improve fracture healing and also may improve physical function (using the Timed Up and Go test).[8] Recent reviews and case series of TPTD and fracture healing state that there is a potential benefit of TPTD but all conclude that further randomized, placebo controlled, clinical trials are warranted.[26-30] An important additional question is whether the benefit of TPTD on fracture healing wanes over time. In a recent study, improved mobility was seen at 3 and 6 months but not 12 months in TPTD treated patients with unstable pertrochanteric fractures,[16] making a longer follow-up important in the proposed trial.

In summary, pelvic fractures are costly for both the individual and society due to the lack of surgical intervention and the long time to heal, making this an ideal fracture to use in a study of fracture healing. In addition, the lack of surgical repair means that the effects of TPTD on fracture healing cannot be confounded by a surgical procedure. Although both TPTD and (1-84PTH) have been shown to lead to some improvements in fracture healing, a randomized double-blinded placebo controlled clinical trial is now needed to confirm and extend any beneficial effects of TPTD on the acceleration of fracture healing. Additionally, since the pelvic bone has a higher proportion of cancellous bone and thinner cortical walls than long bones[31,32] and TPTD increases bone mass most effectively in cancellous bone,[22,33] pelvic fracture might be particularly amenable to accelerated fracture healing with TPTD. The TPTD or placebo would be administered in addition to current standard of care for pelvic fractures, which includes pain management, patient mobilization, and the prevention of complications associated with comorbid conditions.[7] Given that pelvic fractures are an osteoporosis related complication and represent severe osteoporosis, we recommend treating all pelvic fracture patients for the underlying disease of osteoporosis. Therefore, after the 3 month trial, we will offer all study participants a year of open label TPTD. Since the optimal time to initiate osteoporosis treatment is when the patient has a fragility fracture, clinicians need to know if the drug is neutral or accelerates fracture healing. If the current study clearly demonstrates enhancement of fracture healing, the fracture team will be more motivated to start osteoporosis care (currently < 20% of patients get treated).[34] Therefore, any evidence that fracture healing is improved with TPTD would markedly change the clinical care of this fracture. Furthermore, any benefit of TPTD to healing of pelvic fractures, may serve as a model for the study of other osteoporosis fractures.

At this time, there are no currently approved drugs for fracture healing. Therefore the premises for this trial include: (1) the need for a treatment for pelvic fractures that cannot be surgically repaired, (2) the need to study fracture healing in a well-designed placebo controlled, double blind, randomized trial to determine whether the findings of Peichel et al[8] can be confirmed (3) to determine if 1-34hPTH can improve fracture healing similarly to findings with 1-84PTH (4) to corroborate pre-clinical data, findings from case series, and trials which suggest that TPTD may accelerate fracture healing. If the results of this trial are positive with more rapid fracture healing and potentially quicker return to normal physical function; we anticipate that more pelvic fracture patients would be appropriately treated for their osteoporosis post-fracture. In addition, a positive finding may have a dramatic impact on clinical care of patients with other osteoporosis related fractures.

Preliminary and published data strongly recommend TPTD as a bone anabolic therapy to treat the underlying osteoporosis, the ultimate cause of the fracture. The patients enrolled in this trial would all be eligible for an osteoporosis treatment with TPTD being an excellent choice. We believe there will be an added benefit of TPTD beyond the treatment of osteoporosis, including radiographic evidence of accelerated fracture healing, a quicker improvement in physical function, and a faster reduction in pain. The risks associated with the study include the potential side effects of TPTD and the radiation dose from plain x-rays and CT scans.

However, during our prior NIH planning grant (U34), we developed a technique to lower the radiation exposure in this study to be lower than that typically associated with standard care.

4. Study Design:

Overview: In the proposed phase 2 study, we plan to evaluate if treatment with TPTD 20 mcg daily compared with identical appearing placebo, both with the standard management of non-surgical pelvic fractures (pain management, bed rest and prevention of complications from comorbid conditions), is effective in accelerating fracture healing. This is a prospective randomized, double-blinded, placebo-controlled 3 month study of the efficacy of TPTD in postmenopausal women and men ≥ 65 years of age with acute fractures of the pelvis. Our primary outcome is radiographic evidence of fracture healing using low dose Focus CT at 3 months. Secondary outcomes include assessment of pain and narcotic use, and assessment of lower extremity physical function at 3 months and again from 3-12 months. We will randomize 100 patients 1:1 in a blinded fashion to receive either 20mcg of TPTD subcutaneously (SC) every day or identically appearing placebo SC for 12 weeks. All patients will have ideal medical care for comorbidities, pain management and progressive mobilization. A routine clinical protocol will be followed to quickly normalize 25-hydroxyvitamin D (goal >20 ng per milliliter; the current IOM guideline 2010[35]) before starting treatment. All patients will receive a loading dose of vitamin D_2 (at a dose of 50,000 IU given orally[36]) following the protocol used by Lyles et al to normalize vitamin D in a clinical trial of similar patients with acute hip fracture.[36] After the loading dose, daily supplementation with 1000 IU vitamin D will be used for the duration of the study. This will allow for patients to be recruited and to begin the trial of TPTD or placebo within 1 month of the fracture with improved 25(OH)D levels. Calcium intake will be assessed and dietary suggestions or supplementation will be used to bring total intake to approximately 1000 mg a day, slightly lower than the recommended calcium intake for women over age 50 (in order to prevent hypercalcemia).

Subjects

Inclusion criteria: Postmenopausal women and men ≥65 years of age with acute pelvic fractures, occurring with minimal trauma, presenting to Helen Hayes Hospital, Lenox Hill Hospital, New York Presbyterian-Queens, Hospital for Special Surgery, or New York Hospital (Cornell Medical) within one month of the onset of symptoms. Since 25% of pelvic fractures occur in men, it is important to include men in this trial. The inclusion of males will also extend the results of the Aspenberg[14] and Peichel[8] trials). Given that 53% of fractures have an associated injury in the posterior pelvic ring,[37] it is important to include these multiple rami fractures. Patients that have either one or multiple pelvic fractures or sacral and pelvic fractures will be included in the study.

Exclusion Criteria:

1) Persons unable to complete the NRS and other surveys based on their mini-mental status score (≤18; consistent with moderate and severe cognitive impairment)
2) Previously (prior to fracture) non-ambulatory subjects
3) Exclusion criteria related to contraindication or intolerance to TPTD:
    a) Hypersensitivity to TPTD
    b) Patients with increased risk of osteosarcoma: Paget's disease, history of radiation exposure
    c) Patients with active hypercalcemia
    d) Current hyperparathyroidism and other metabolic bone disease including osteogenesis imperfecta
    e) History of multiple renal calculi or renal calculus within the last 2 years
    f) Normal alkaline phosphatase levels will not be used as an entrance criterion because most fracture patients will have elevations due to the acute fracture. However, we will attempt to obtain lab tests from the period prior to fracture to determine if they were normal. If unexplained elevations in alkaline phosphatase are found in labs prior to the fracture we will exclude that subject.
    g) Evidence of metastatic cancer or history of bone cancer or any active cancer other than basal or squamous cell carcinoma.

Protocol:

Recruitment:

Subjects will be recruited, during their initial hospitalization (median length of stay is 9 days[1]) or from the emergency room or physician office from Hospital for Special Surgery/New York Hospital, Lenox Hill Hospital, New York Presbyterian Queens, or Helen Hayes Hospital. The goal will be to start treatment within one month

of fracture. Since not all pelvic fractures are hospitalized,[1] radiologists at each institution have agreed to contact us regarding patients with pelvic fractures who are not admitted. We will recruit approximately 100 subjects (female and male) $\geq$ 65 years of age over a total of 4 years (30 in years 1, 2 and 3 and 10 in year 4) to complete 80 subjects with 3 months of treatment, to accommodate a drop-out rate of 20% in the 3 month treatment portion of the study.

Screening and Baseline visit: Subjects will have their screening and baseline visit during their initial hospitalization or by coming into one of the participating hospitals for a follow-up orthopedic or outpatient visit for those with documented pelvic fractures who were not hospitalized.

Screening visit: At the screening visit, a Mini Mental Status Exam (MMSE) will be given to be sure that the patient is capable of providing informed consent and of completing the trial. Any persons with moderate or severe cognitive impairment will be excluded (score ≤18 of 30 points). The consent form will be reviewed and signed. A comprehensive assessment of medical history and a brief physical exam will be performed. Blood samples will be obtained and levels of creatinine, alkaline phosphatase, calcium, intact-parathyroid hormone, and 25(OH)D will be measured. Pelvic radiographs and a full CT scan will be reviewed or obtained to determine if fractures are: single rami, multiple rami fractures or sacral and pelvic fractures (healing of sacral fractures will not be assessed, although the existence of a sacral fracture with a pubic rami fracture will not exclude an individual). In addition, the fracture will be classified by amount of displacement/overriding with 3 categories: Minimal/No displacement, Mild displacement, Moderate displacement.[38] A loading dose of vitamin D (50,000 IU) will be given[36] in order to normalize vitamin D in this population with high prevalence of vitamin D deficiency before initiating treatment (goal within 2 weeks of the fracture). Serum calcium must be below or equal to normal for the lab. Calcium supplements or dietary modifications will be recommended as needed to bring total calcium intake to approximately 1000 mg daily. Subjects who meet all inclusion and exclusion criteria based on labs and history will be scheduled for a baseline visit. Concomitant medications and existing baseline conditions will be collected by interview. Information about the use of prior osteoporosis treatment will be obtained and recent BP use will be categorized for randomization.

Baseline Visit: Baseline visits will be scheduled when all results are in and within one month of fracture. Subjects will be seen in the morning after an overnight fast. Blood will be drawn and subjects will be allowed breakfast. Vitamin D supplements (1000 IU daily) will be provided to help to maintain adequate 25OHD serum levels and calcium intake will be reviewed. A blood sample will be collected at baseline and at every visit to assess calcium level for safety. Blood samples for biochemical indices of bone turnover (serum PINP for bone formation and serum CTX for bone resorption) and 25(OH)D will be obtained at baseline and every month and analyzed by batch at the Helen Hayes Hospital Regional Bone Center. Subjects will complete the lower extremity physical function tests, an Activities of Daily Living (ADLs) and SF-36 physical function survey, NRS for pain and a survey with pill count to determine narcotic use. Subjects will be randomly assigned (with separate schemes for males and females and prior BP use) to receive either TPTD 20 mcg or identically appearing placebo. Only the statistician will be aware of subject assignment and the pharmacist will distribute the appropriate TPTD or placebo medication. Subjects will be taught by the research nurse the method of daily self-administered subcutaneous injection techniques using TPTD or placebo pens, and provided written instructions for drug administration with a diary to track injections. We have extensive experience teaching subjects to administer TPTD with >90% compliance in elderly populations[21,33,39,40] and subjects in the modelling recruitment phase were willing to take TPTD. Treatment will continue for the 3 months of the proposed study. Even if the fracture heals sooner, these subjects all have osteoporosis and should maintain their osteoporosis treatment for the duration of the double blind trial while other outcomes are evaluated (0 to 3 months).

Retention: Subjects will be called weekly during the 3 month blinded trial to monitor side effects and adverse events, and to ensure compliance with the protocol, including medication adherence.

Follow-up visits: All visits will occur at the center where the subject was recruited and would normally be seen, following the schedule of procedures listed in Table 2. Visits will occur every month for 3 months. At every visit a pelvic radiograph will be taken. If the radiologist notes cortical bridging on pelvic x-ray, then a confirmatory low dose Focus CT at the fracture site(s) will be performed to assess the degree of bridging at the

fracture site(s). If full union is noted at the superior and/or inferior pubic fracture site(s) by focus CT, as evaluated by both radiologists, then no further radiographs or CT scans are needed, although all other assessments will continue. The CT will be done at either Ramapo Radiology in Suffern or MRI in New City, NY. At 3 months the remaining patients who still have not healed will undergo a focused limited low dose CT to quantify the degree of cortical bridging at the end of the 3 months of placebo-controlled treatment. In addition, radiographic follow-up will continue during the open label extension for those patients who have not healed during the 3 month active treatment phase.

Blood samples to assess bone turnover and calcium levels will be collected as indicated. Subjects will be encouraged at each visit to consume enough calcium and vitamin D (1000 IU vitamin D and dietary calcium with supplements as needed) and TPTD/placebo compliance will be assessed.

At each monthly visit (0 to 3), subjects will complete the lower extremity physical function test, ADLs, SF-36, NRS for pain and a narcotic use survey and pill count (details below). This information will be recorded by a research nurse blinded to treatment status since TPTD and placebo will be identical in appearance. Lower extremity physical function test, ADLs, SF-36, NRS for pain and a narcotic use survey and pill count will be repeated at 6, 9 and 12 months visits to determine if starting TPTD immediately after fracture results in better long term changes in function and pain, although the extension will be open label with all offered TPTD and analyzed as a separate secondary outcome (3 to 12 month; see below).

Withdrawals: Any subject who wishes to withdraw from the study will be asked to return any study drug and, if willing, to complete the lower extremity physical function test, ADLs, SF-36, NRS for pain and a survey and pill count of narcotic use. They will also be asked to get a final x-ray and focus CT if they consent and there has not been one within a month.

Randomization and Medication: This study is being performed under IND 126129 with Jeri W. Nieves, PhD as the sponsor. Within one month of the onset of symptoms, all subjects will be given either (1) TPTD or (2) TPTD- placebo for 3 months. Eli Lilly has agreed to provide TPTD and matching placebo in order to mask treatment for the double blind study. TPTD is supplied as a sterile, colorless, clear, isotonic solution in a glass cartridge which is pre-assembled into a disposable delivery device (pen) for subcutaneous injection. Each prefilled delivery device is filled with 2.7 mL to deliver 2.4 mL. Each mL contains 250 mcg teriparatide (corrected for acetate, chloride, and water content), 0.41 mg glacial acetic acid, 0.1 mg sodium acetate (anhydrous), 45.4 mg mannitol, 3 mg Metacresol, and Water for Injection. In addition, hydrochloric acid solution 10% and/or sodium hydroxide solution 10% may have been added to adjust the product to pH 4. The placebo pen contains the same solution without the TPTD. Medication pens must be refrigerated after each daily use. Compliance will be assessed by review of subject injection diaries and by weighing returned TPTD/placebo pens.

Randomization will be by gender and bisphosphonate (BP) use creating 4 randomly permuted block randomization lists. We will not exclude prior BP use, however, since the recent use of BP may impact TPTD effect, BP use will be used to create the following strata for randomization within males and females: (1) Recent BP use (greater than one year use within 2 years)/female or (2) Recent BP use (greater than one year use within 2 years)/male (3) distant or never ($\geq$ 3 years since last BP or never users)/female (4) distant or never ($\geq$ 3 years since last BP or never users)/male. We hypothesize that acceleration of pelvic fracture healing by TPTD will not be significantly affected by prior BP use because this skeletal site is largely cancellous bone and we believe that TPTD response is less affected by prior BP use in primarily cancellous sites (vs cortical sites).[41] In addition, initial fracture healing is dependent on callus formation which is not diminished by BP.[42] Furthermore, there was no significant difference in delayed union of the fractured bone between placebo and zoledronic acid after hip fracture.[36] However, given the potential for recent BP use to alter BMD and turnover response to TPTD,[39,43,44] we will stratify by BP use to ensure that any effect of BP on TPTD is equally distributed between the placebo and TPTD groups. In addition, we will record length and type of bisphosphonate use as a potential covariate in the analysis to evaluate effect modification by prior BP use.

Open Label Extension: After 3 months of placebo versus TPTD, when the data for the primary analysis of all aims has been collected, all persons will be offered to continue TPTD (open label) for 9 months while pain and physical performance are assessed and surveys completed every 3 months. The open label protocol will allow

for an evaluation of the persistence of any potential benefit of TPTD on fracture healing (assuming that one is evident after the first 3 months) on functional outcomes. We believe offering open label TPTD after the 3 months placebo controlled blinded trial will also help aid in the recruitment of patients since they will all eventually be treated and the extension follows guidelines to treat patients with pelvic fracture (consistent with severe osteoporosis). During the open label extension, the ~32% of the control group that may not have healed at 3 months will be followed with radiographs to enable us to determine the time to heal in this group. Treatment with open label TPTD may accelerate their healing and mitigate the difference in the secondary aim of functional outcomes between groups during the latter part of the year (3-12 months). However, we believe most of the effect on the secondary outcomes of physical function and pain would have occurred in the first 3 months for most people and modest changes will only occur in a few patients. We hypothesize that differences seen between PBO and TPTD groups at 3 months will persist when evaluated up to 12 months. This will be assessed as a group by time interaction. This extension will add to the data on pain and physical function collected at the end of the double blind trial (0 to 3 months). If the natural history cohort is large enough we would also be able to see if the TPTD over 3 months, with continued treatment for the subsequent 9 months improves physical function more than no treatment over the year. The open label extension will allow us to determine whether our hypothesis of faster healing by TPTD (at the end of 3 months) produces a long term benefit of improved function between 3 and 12 months, or if the effect wanes within that group. Evidence of a better result if TPTD is started immediately may enhance treatment rates post fracture.

5. Safety:

Total serum calcium will be assessed at baseline for study eligibility and then at every visit via standard automated chemistry. Avoiding excessive calcium supplements will help prevent hypercalcemia, therefore we will assess diet and use supplementation only to obtain a total intake of 1000 mg daily. Serum calcium will be reviewed by our safety officer (Dr. Emily Stein at HSS). A preplanned algorithm for hypercalcemia (defined as >10.1 mg/dl, the upper limit for our laboratory) requires stopping calcium supplements or reducing dietary intake and repeating the measurement within 2 weeks. If hypercalcemia persists, TPTD/placebo will be withheld. At each monthly visit and during the weekly phone calls while on TPTD/Placebo, adverse events (AEs) or serious adverse events (SAEs),comorbidities and concomitant medication use will be recorded by the nurse and reviewed with the site MD (RN and MD are blinded to treatment). Follow-up for any SAE will occur until it is resolved. All SAEs will be reported to the internal safety officer (Dr. Stein) and to the DSMB safety officer and NIAMS (through KAI) within 48 hours of the investigator becoming aware of the SAE. The IRB and FDA (IND 126129; Dr. Nieves) will be notified of SAEs as per their guidelines. The radiographic evaluations will expose subjects to radiation, however this will not exceed normal clinical care and in fact we worked to reduce exposure using our protocol for focus CT imaging. Dr. Emily Stein will serve as the internal safety officer for this study and will review all AE, SAEs and serum calcium for safety. In addition, there is a 3 person DSMB for this study that was appointed by NIAMS. The DSMB will receive reports from the study team every six months for additional safety review. Annual reports will also be filed with the FDA, IRB and NIH.

6. Data and Safety Monitoring Responsibilities:

Data and safety monitoring will be the primary responsibility of all persons with patient contact, the research nurse and other staff, Dr. Lane and Dr. Nieves. In addition, Dr. Stein will review the serum calcium safety labs for any evidence of hypercalcemia and will review all AEs and SAEs. Dr. Nieves in cooperation with the research nurse and site investigator will be responsible for reporting these events to the internal safety officer and to KAI who will distribute to the DSMB safety officer and NIAMS. They will also be sure that each IRB and the FDA are notified.

For any unanticipated problems or serious adverse events, including hospitalizations, cancers or deaths, the internal safety officer and KAI who will distribute to the DSMB safety officer and NIAMS within 48 hours of learning of the complication. The IRB and FDA (IND 126129; Dr. Nieves) will be notified of unanticipated problems and SAEs as per their guidelines.

Teriparatide: We will initially minimize risks of teriparatide treatment by excluding subjects who might be at higher risk for adverse events. The risks of subcutaneously administered teriparatide injections include local skin irritation, dizziness, leg cramps, nausea, arthralgias, myalgias, hypercalcemia and hypercalciuria.

Although no increase in risk of renal stones has been seen in clinical trials with teriparatide, potential subjects with recent kidney stones (within 2 years) or a history of multiple stones will be excluded from the protocol to minimize this risk. Because teriparatide treatment has a boxed warning regarding risk of osteosarcoma, potential subjects who have an increased risk of osteosarcoma, such as those with Paget's disease, prior history of bone tumor, or history radiation therapy will be excluded from participation in the trial. Also, to minimize risk of hypercalcemia or hypercalciuria, potential volunteers with evidence of hyperparathyroidism will be excluded from participating in the trial. To monitor any occurrence of adverse events, side effects, or difficulty with medication administration with TPTD, subjects will be called weekly by the Research Nurse during TPTD treatment. In cases where side effects are significant and interfering with quality of life (e.g. musculoskeletal pain or nausea), volunteers will be told to reduce TPTD administration to every other day until the symptoms abate.

Monitoring of Hypercalcemia: The major safety evaluation of this study is a check for hypercalcemia which will first be assessed at 4 weeks after starting TPTD when calcium levels are found to peak. The development of hypercalcemia may be dependent on an individual's baseline serum calcium level and calcium supplement exposure. Therefore, volunteers will be counseled by the Research Nurse about optimizing dietary calcium intake, and avoiding calcium supplement use in order to prevent the development of hypercalcemia. Calcium supplements will be used only as needed to bring daily calcium intake to 1000 mg a day. Serum calcium levels will be checked at every visit, which occur monthly for the first 3 months after TPTD or placebo initiation and then, during the open label with teriparatide treatment, levels will be checked every three months. Subjects will be advised not to take the TPTD or placebo prior to the blood sample being collected (levels will be obtained at least 16 hours after the last TPTD dose). Serum samples will be analyzed within 24 hours of sample procurement and will be reviewed by the Safety officer (ES) within 24 hours of receipt of result.

If the serum calcium is above 11.5 mg/dl, calcium supplements or dietary calcium will be reduced and the level will be checked again within 3 days. If the level remains >11.5 mg/dl; TPTD will be given on alternate days.

If the serum calcium is between 10.5 and 11.5 mg/dl, calcium supplements or dietary calcium will be reduced and the level will be checked again within 10 days. If serum calcium levels are persistently above 10.5 mg/dl, volunteers will be advised to take TPTD every other day.

In multiple prior trials involving TPTD treatment in hundreds of patients, we have never been required to reduce the dose of TPTD due to hypercalcemia.

7. Protocol Details:

Case-Report Forms: Case report forms will be used to record screening information, medical history, medication list and lifestyle information (including calcium intake) and the physical exam. The nurses will complete forms for AEs, SAEs and concomitant medications. All AEs and SAEs will be reviewed with the study MD at each site. Standardized forms will also be used for the outcomes: radiologic evaluation of fracture healing, NRS for pain and narcotic use, lower extremity physical function.

Table 2: Schedule of Procedures

Procedure	SCR	D1	4 wk	8 wk	12 wk	6 mo	9 mo	12 mo
MMSE, Informed consent	X							
Medical history, medication list and other lifestyle	X							
Physical examination, including height and weight	X							
Screening labs (25(OH)D, PTH, Cr, Ca, prior alkaline phosphatase)	X							
Pelvic radiographs (^until healing occurs-standard care)	X		X^	X^	X^			
Pelvic limited focus CT scan (* as indicated based on cortical bridging and until healing occurs)	X full		X*	X*	X*			
Bone turnover		X	X	X	X			

Calcium for safety		X	X	X	X	X	X	X
Loading dose vitamin D (50,000 IU)	X							
Calcium (total intake 1000 mg) /1000 IU vitamin D		X	X	X	X	X	X	X
Dispense TPTD 20 mcg/day or placebo (blinded for 3 months, then open label TPTD)		X	X	X	X	X	X	X
Adverse event and concomitant medications		X	X	X	X	X	X	X
Numeric Rating scale (NRS) for pain and narcotic use survey and pill count		X	X	X	X	X	X	X
Lower extremity physical function (CSPPS and TUG)		X	X	X	X	X	X	X
Self-reported questionnaires (ADL and SF-36)		X	X	X	X	X	X	X
Telephone calls will occur weekly			X	X	X			

Specific Methodology:

CT imaging: The first CT image that identifies the fracture will be a standard pelvic CT. For follow-up CT imaging, we will utilize a novel method to assess fracture healing (Focus CT). Presently, plain radiographs and serial computed tomography are completed every month, a with a radiation dose of 7.5 mSv per exam. [70-73] Focus CT, which will reduce radiation exposure, could be used in place of standard serial CT to assess the healing process. A low dose technique[74,75] using an automatic tube current modulation (ATCM) technique was developed for the pelvis, making it possible to achieve a reduction in radiation dose to the patient.[76,77] It is important to reduce medical radiation exposure as much as possible, the "as low as reasonably achievable" (ALARA) concept, which could be achieved by utilizing Focus CT scanning to the area of specific interest e.g. limiting radiation exposure to the fracture site alone.[78] Focus CT is accomplished by decisions regarding the collimation, pitch, tube voltage, current, and rotation and by reducing the scan field of view. Scanning a smaller Field of View (FOV) alone resulted in an estimated reduction of radiation exposure of between 40-68% relative to a standard full FOV CT of the pelvis. Additionally, there was no difference in the diagnostic quality of the Focus CT relative to the baseline full FOV CT for tracking fracture healing, with both musculoskeletal radiologists noting a 100% intra-observer concordance in their findings between the full FOV and Focus CT images for each case.

Initial CT Scan: After obtaining frontal and lateral topograms of the pelvis (120 kV; 10 mA), helical CT of the pelvis will be obtained from the L5 vertebral body through the ischia without intravenous contrast (GE Light Speed Pro 32 CT). Scans at both sites will be obtained following the same protocol with slice thickness of 2.5 mm, interval of 1.25 mm, keV of 120, and Auto mA with range of 100-500 and noise index of 15.17. Sagittal and coronal reformats will also be created and reviewed. The initial CT scan will define all pelvic fractures including pubic rami and sacrum. The fracture will be classified as: single or multiple rami fractures; presence of sacral fracture and amount of displacement with 3 categories: Minimal/No displacement, Mild displacement, Moderate displacement.[38]

Focus CT Scan (Follow-up): After obtaining frontal and lateral topograms of the pelvis (120 kV; 10 mA), focused helical CT will be obtained from 1 cm above the superior pubic ramus to 1 cm below the inferior ischiopubic ramus without intravenous contrast (GE LightSpeed VCT). Scans will be obtained with a slice thickness of 2.5 mm with interval of 1.25 mm, keV of 120, and Auto mA with range of 100-500 and noise index of 15.17. Sagittal and coronal reformats will also be created and reviewed. The focus CT will only evaluate superior and inferior pubic fractures, since CT determination of sacral fracture healing is difficult.

At any visit where some cortical bridging is noted on the x-rays, a CT is performed and cortical bridging will be quantified with bridging of 3 or 4 cortices as "healing", 1 or 2 cortices with "partial healing", and 0 cortices with "minimal/no healing".[45] If there are multifocal fractures, cortical bridging at each site will be evaluated and an average of cortical bridging score (0 to 4) will be recorded. If full union is noted by focus CT (evaluated by both radiologists), then no further radiographs or CT scans are needed, although all other assessments will continue. At 3 months the remaining patients who still haven't healed will undergo a focused limited low dose CT to quantify the degree of cortical bridging after 3 months of treatment. Radiographs and CT scans will continue during the open extension in those who have not yet healed. CT scans will be evaluated independently by Drs. Loftus and Bartolotta, who will be blinded to treatment group. If there is a discrepancy between the score for cortical bridging (1 score difference in the reading) between them, a third reader as part

of the Contract Imaging Coordinating Center role at Weill Cornell Radiology will be brought in to blindly adjudicate the discrepancy. All CT images will be de-identified and archived using IDEAL (Imaging Data Evaluation and Analytics Lab) that houses the research PACS system with individual data devoid of any PHI and only having a subject ID.

The research nurse will record the pain assessment, administer physical performance tests using standard methodology and administer all surveys as detailed below. **Pain assessment:** The research nurse will administer the NRS for pain. Using a scale from 0 (no pain) to 10 (worst pain imaginable), the subject will report how intense their pain is now and how intense it was on average last week. They will also report how much relief from pain they have achieved using treatment for pain. For this they will use a scale of 0% (no relief) to 100% (complete relief). They will also be asked about all of the pain medications they are currently taking. In addition, the nurse will ask the subject to bring any pain medications being used to each visit so that a pill count of use can be made. **Physical Performance Measures[49-64]:** The **walk** is a timed walk at normal walking speed with a meter run-in before starting the timed portion and another meter at the end of the course in order to measure each subject walking at normal speed over 4 meters. Devices such as canes and walkers are allowed and their use will be recorded. The research nurse will record the use of aids and the time required to walk on the case report form. A straight backed chair will be placed against a wall and subjects will be asked to stand with their arms folded across their chest. If they can perform this task they will be asked to repeat it five times. The research nurse will record the amount of time for 5 **chair stands** to be completed on the case report form. The **balance test** measures the ability of subjects to maintain balance for 10 seconds in each of 3 positions: side-by-side, semi-tandem, and tandem foot positions. The test will be stopped if the subject cannot maintain any position for 10 seconds. The final measure for balance is the sum of the time from the three positions (range 0-30 seconds). Subjects unable to perform any of the above three tests will be assigned a 0 score. During the course of the balance test there will be two trained individuals standing in an appropriate manner to protect a patient against any falls. The research nurse will complete the case report form and follow written instructions in the detailed clinical protocol. Scores will be calculated for the CSPPS based on these tests.[66-68] ***Timed Up and Go Test (TUG)[69]:*** Patients will be asked to wear their regular footwear and told that they can use a walking aid if needed (this will be recorded). The test begins by having the subject Stand up from the chair, walk to the line on the floor at a normal pace, turn, walk back to the chair at a normal pace and Sit down again. The person administering the test will time the subject using a stopwatch and record the time on case report forms.

Surveys: All performance tests and surveys will be administered by the research nurse, who is blinded to treatment status during the study visit. Study participants will complete several questionnaires, including assessments of ability to perform activities of daily living (ADLs)[79] and the physical component of SF-36.[80,81] The Barthel activity of daily living (ADL)[79] survey is a patient self-reporting survey to assess mobility and self-care. Subjects are asked a series of questions and asked to respond with a multiple choice answer about difficulty the level of difficulty with which they are able to complete each task, the baseline ADL will evaluate pre-fracture and current ADLs. For the assessments of ADLs, subjects will report 1 of 3 responses, similar to those used in WHAS[82]: 1) no difficulty, 2) little of some difficulty, 3) a lot of difficulty or unable to do without help from a person or special equipment. For the SF-36, only the physical sub-scales will be used: Physical Function (PF), Role-Physical (RP), Bodily Pain (BP), and General Health (GH).[80,81] Subjects will be asked questions about general health and physical limitations over the previous 4 weeks (before the fracture during screening and then since the fracture will be asked at baseline). All responses are recorded CRF and scored.

Biochemistry: After blood samples are obtained, all processing and aliquoting procedures are performed in the Biochemistry Unit of the Regional Bone Center of Helen Hayes Hospital. Biochemical evaluations will include those used for exclusion criteria, efficacy (bone turnover) and safety (serum calcium). All efforts are made to prepare aliquots according to the assays planned to avoid repeated thawing and refreezing. For this project, serum samples for bone turnover (PINP and CTX) and serum 25(OH)D will be stored in separate 1 ml aliquots in a -80 degree freezer. All biochemical efficacy assays from an individual patient will be performed in the same assay to avoid inter-assay variability in individual patients. All assays planned in this proposal have been performed for a number of years in the RBC Laboratory. Specific methods and quality control data for each assay have been previously reported.[21,33,39,40]

Data Management: Subjects will be enrolled at each Hospital with each site having a dedicated research coordinator. All identifying information will be kept on one form in a locked file cabinet at each site along with the consent form. A study ID number will be given to each person and completed CRF's will be sent to the

data manager on paper. We will enter these into a Microsoft Access database with built-in logical checks. Site monitoring of the type that is done for multi-site pharmaceutical studies will be completed. Data collection forms have been centrally designed and will be distributed. A case report book for each subject will be prepared to contain each case report form required to be completed according to the protocol. Each case report form has standard header information identifying the study subject by research identifier, when the data is collected, the location where data is collected and a unique identifier signifying the identity of the research staff member responsible for the validity of the data recorded on the form. Forms recording the results of clinical and/or laboratory evaluations will have countersignature by a study physician to attest to the medical review of the data for safety. Data that is de-identified will be entered into the database. While field ranges and valid value codes will be checked in the data entry screen application, central data monitoring programs will monthly summarize data quality: a) recruitment, enrollment and retention; b) visit attendance and missed visits; c) missing forms; d) within form edit checks on item ranges and valid values, skip jumps, and across-item logical consistency checks; e) between form within visit logical consistency checks; f) within form between visit logical consistency checks. A routine suite of reports summarizing the results of the above data quality reviews will be sent back to the research study coordinator at each site and progress at correction or documentation of suspicious values will be monitored through edit review and the next month's reports. The PI and Co-PI will be kept appraised of data quality and targets for data timeliness, accuracy and documentation quality will be presented and periodically reviewed with research staff. Error checking programs written in SAS, will be run periodically. All data will be imported into SAS for analysis. The database and randomization list will be password protected, and backed up daily.

Statistical Plan: There will be no interim analysis and missing outcome data will not be imputed. Statistical analysis will be performed using SAS software (Cary NC). Between group differences at baseline will be compared with t-tests or Wilcoxon rank sum tests and chi-square tests as appropriate (p-value <0.05 for significance). Randomization by the method of randomly permuted blocks will be created for gender and BP use groups. Our primary analysis is ITT analysis and our primary outcome (SA#1) is the categorization of the level of bridging seen on focus CT into the scores from 0 to 4, described above between 0 and 3 months. The difference in cortical bridging will be evaluated by a 2x5 chi-square (group x score) with a trend test (Jonckheere-Terpstra)[83] to see whether TPTD treated "trend" to have more higher bridging scores than the placebo group. We expect 30% - 50% superiority with TPTD at 3 months. This categorical outcome will be further analyzed with generalized estimating equations (GEE) for longitudinal repeated measures assuming a Poisson distribution with weighting from logistic regression analysis of the missingness pattern. Secondary analyses of covariates, sensitivity analyses and the "per protocol" analysis will incorporate the aforementioned approach into this aim's GEE analysis. This analysis addresses the question "Do patients treated with TPTD show more rapid fracture healing than those given placebo? For SA #2, we anticipate that the difference in pain score between the TPTD and placebo groups in the proposed study will be > 30% at each monthly time point (0-3 months). We will use a between-groups linear mixed model for repeated measures (LMMrm) to estimate the primary outcome of the difference in the mean within-subject change from baseline in the two groups at the end of the placebo controlled trial (0-3 months) and again to explore change from 3 to 12 months in the open label extension. In addition, narcotic and non-narcotic pain medication use will enter the model as time-dependent covariates. This analysis addresses the two questions, "Do patients treated with TPTD show more rapid reduction in reported pain level than those not so treated? If so, when?" For SA#3, the CSPPS is the outcome. A linear mixed model for repeated measures (LMMrm) will be used with fixed effects of treatment group (TPTD vs. placebo), time (D1, 4-, 8- and 12-wk) and their interaction, the baseline level of the CSPPS and days from injury to randomization entered as covariates, and a within-subject covariance structure selected by empirical methods prior to hypothesis testing. This plan will be repeated for the "per protocol" analysis in which subjects are limited to those showing 80% or greater compliance over the 12-week trial. This statistical plan addresses the two clinical questions, "Do patients treated with TPTD recover lower limb function faster than those not so treated? If so, when?" LMMrm will be used to analyze data from 3-12 months and assess group by time interaction. We will group on prior BP exposure strata to account for possible heterogeneity in the R-side covariance structure.

Imbalances in group characteristics at baseline (p-values < 0.20) will be assessed as covariates in secondary analyses and findings of significant effect modification will be followed-up with sensitivity analyses. Cumulative

exposure to treatment will be entered as time dependent random effect to incorporate compliance and non-completer data. Other outcomes will be similarly analyzed in secondary analyses. The following variables will be considered and tested as potential covariates in these models using $p<0.2$ correlation with outcome as criterion: gender, age, baseline 25(OH)D, pre-fracture SF36 physical function score, Charlson Comorbidity scale, concomitant medications, recent BP use, fracture severity (displacement) and fracture category (single or multiple fractures or sacral and pubic).

Sample Size Justification: We will recruit 100 female and male subjects over 4 years (30, 30, 30, 10) to yield 80 analyzable subjects completing 3 months of treatment after assuming a 20% overall drop-out rate. Power and sample size were calculated for SA#1 fracture healing by radiographic studies: if 100% of TPTD and 60% of placebo have completed fracture healing by three months, 40 subjects per group provides > 95% power with 1% alpha to detect this difference based on an analysis of proportions. For the Timed Up and Go Test assuming Peichel's results (at week 12 TPTD = 22.9 $\pm$ 7.7 vs Placebo = 54.3 $\pm$ 19.9), a SD of 18 and a week 4 to 12 pattern of rapid fracture healing in the TPTD group (at week 8 100% vs 9% in Placebo). A repeated measures ANOVA with a Hotelling-Lawly F-test, the same as the Wald test in the LMMrm model with unstructured covariance matrix, shows 90% power at 1% alpha is achieved for the fixed treatment effect with 33 subjects per group and time-by-treatment interaction with 36 subjects per group (SAS 9.4 GLMPOWER).