Phase 2 Study of Teriparatide for the Treatment of Idiopathic Osteoporosis in Premenopausal Women

IRB AAAF2251
Protocol Version 3.2

1. Study Purpose and Rationale

Osteoporosis is a skeletal disorder characterized by reduced bone strength that predisposes to an increased risk of fracture[1,2]. Osteoporosis affects postmenopausal women and elderly men and is very unusual in healthy individuals under age 50. Moreover, more than 90% of young men and premenopausal women with osteoporosis have a secondary cause of bone loss[3], such as an underlying disorder (e.g., hypogonadism) or a medication exposure (e.g., glucocorticoids, antiepileptic drugs), that either interfered with acquisition of peak bone mass or caused excessive bone loss thereafter[3-15]. Idiopathic osteoporosis (IOP) is defined as osteoporosis that affects young, otherwise completely healthy individuals with intact gonadal function and no secondary cause of bone loss. First described by Fuller Albright in 1944[16], IOP is an uncommon condition with an estimated annual incidence of 0.4 cases per 100,000[3]. IOP predominantly affects Caucasians, who generally present in their mid-30s with one more low trauma fractures[17].
In the course of an NIH-funded study of premenopausal women with IOP (R01 AR49896, IRB AAAA9245), we have shown that women with IOP have low areal bone mineral density (aBMD) at the spine, hip and forearm compared to normal women[79]. Additionally, using noninvasive high resolution imaging of the central and peripheral skeleton and detailed analyses of transiliac crest bone biopsies, we identified several distinctive and consistent features of bone quality in premenopausal women with IOP: thin cortices, lower trabecular volumetric bone mineral density (vBMD), fewer trabecular plates, fewer and longer trabecular rods, decreased connectivity between rods and plates, lower mineralization density and lower estimated stiffness of cancellous bone [80, 81, 82, 83]. Bone remodeling and biochemical indices of mineral metabolism did not differ between IOP subjects and controls [82].

Although not every woman with IOP requires pharmacologic intervention, many have sustained multiple low-trauma fractures or have extremely low bone mineral density (BMD). There is currently no FDA-approved therapy for IOP in premenopausal women and a safe and effective therapy is urgently needed. Bisphosphonates are one therapeutic option, but the associated gains in BMD are primarily due to reduction in the remodeling space and increased mineralization of bone rather than improvements in microarchitecture. This is an important consideration as microarchitectural deficits are a consistent feature of IOP in premenopausal women, while remodeling activity is most commonly normal or low. Furthermore, potential teratogenic effects limit the safety of bisphosphonates in premenopausal women.

Osteo-anabolic therapy with human recombinant parathyroid hormone 1-34, hPTH(1-34) or teriparatide (TPTD), terms which will be used interchangeably in this proposal, has been shown to improve bone mass and microarchitecture in postmenopausal women and is approved for men with primary or idiopathic osteoporosis, as well as men, premenopausal and postmenopausal women with glucocorticoid-induced osteoporosis. In contrast to bisphosphonates, TPTD increases bone formation and BMD, and increases bone strength by improving bone microarchitecture[18-35]. Moreover, TPTD has been shown to increase BMD in men with IOP[36], in premenopausal women with glucocorticoid-induced osteoporosis (GIOP)[37,38] and to prevent bone loss in premenopausal women with nafarelin-induced acute estrogen deficiency [84.] In addition, we have recently completed a pilot study of TPTD in 21 premenopausal women with IOP, in which there were marked improvements in areal BMD by DXA at the lumbar spine, femoral neck and total hip and bone microarchitecture and estimated strength at the iliac crest over 18-24 months of therapy [72,73,76, 85]. Using high resolution CT imaging, we also found that TPTD increased volumetric BMD and estimated strength at the distal radius and tibia in the same women.

The major objective of this protocol is a therapeutic one, namely to establish the safety and efficacy of TPTD in premenopausal women with IOP in a phase 2 clinical trial. We hypothesize that osteo-anabolic therapy with TPTD will improve areal and vBMD in premenopausal women with IOP. We also hypothesize that TPTD will restore abnormal microarchitecture toward normal and improve other aspects of bone quality in premenopausal women with IOP. The primary aim of this research study will be to establish the efficacy and safety of 6 months of TPTD versus placebo in premenopausal women with IOP. Secondary aims are to determine the extent to which 12 and 24 months of TPTD improves areal and volumetric BMD, bone microarchitecture and stiffness compared to baseline measures in premenopausal women with IOP, to assess the effects of TPTD on bone remodeling at the tissue level in women with IOP and to determine whether baseline bone turnover, as assessed by quadruple tetracycline labeling predicts response to TPTD. This study will have high impact on clinical practice as it pertains to the management of premenopausal women with IOP. This study is exploratory and will not support any new labeling claims for Forteo in the premenopausal patient population.

For the sub-study: We aim to investigate the pharmacokinetics (pK) and pharmacodynamics (pD) of teriparatide (Forteo) to determine if subject weight influences pK or pD. To develop preliminary data necessary to plan larger studies on this issue, we aim to study 6 subjects already enrolled in this study (AAAF2251) who are already in the open label treatment period. We will enroll 3 normal weight subjects (BMI between 18.5 kg/m2 and 24.9 Kg/m2) and 3 overweight or obese subjects (BMI equal to or greater than 25 kg/m2). All subjects will be offered participation until enrollment goals for the sub-study will be met.

Previous studies have shown that the increases in BMD observed in response to TPTD may dissipate over time if patients are not placed on antiresorptive therapy after TPTD is discontinued. However, other studies suggest that this dissipation does not occur in women receiving estrogen. Studies in postmenopausal women on estrogen found that hPTH(1-34) increased aBMD at the LS and at the hip[19,33], and resulted in major reductions in vertebral fracture[19]. Importantly, BMD remained stable in postmenopausal women on estrogen followed for two years after TPTD discontinuation[19]. Lane et al. reported similar results in postmenopausal women with GIOP on estrogen[26]. Although no studies have evaluated duration of TPTD effects in menstruating premenopausal women with IOP, an extension study of hPTH(1-34) in premenopausal women with endometriosis receiving nafarelin found that the benefits of in hPTH(1-34) persisted in women who regained normal menses[86]. These three studies suggest that in estrogen-replete premenopausal women with IOP, increases in bone mass resulting from TPTD would be sustained after the course of therapy is completed. However, we recently analyzed new data from our open-label pilot study of 21 premenopausal women with IOP who were treated with 18-24 months of TPTD, 20 mcg daily[85]. Specifically, 2-year follow-up data on 15 of the 21 women, has revealed that nine (60%) have sustained significant bone loss (7.4 $\pm$ 3.1%) at the lumbar spine, although they have maintained the gains at the hip; six women have maintained their gains.

We believe that these data require an amendment to the study design of R01 FD 009302, Teriparatide for Premenopausal Idiopathic Osteoporosis. The current study design includes 12 months of follow-up after the study subjects complete 24 months of TPTD. Instead of the current design, in which all subjects complete one year of observation after 24 months of TPTD, we would like to offer the subjects three choices:

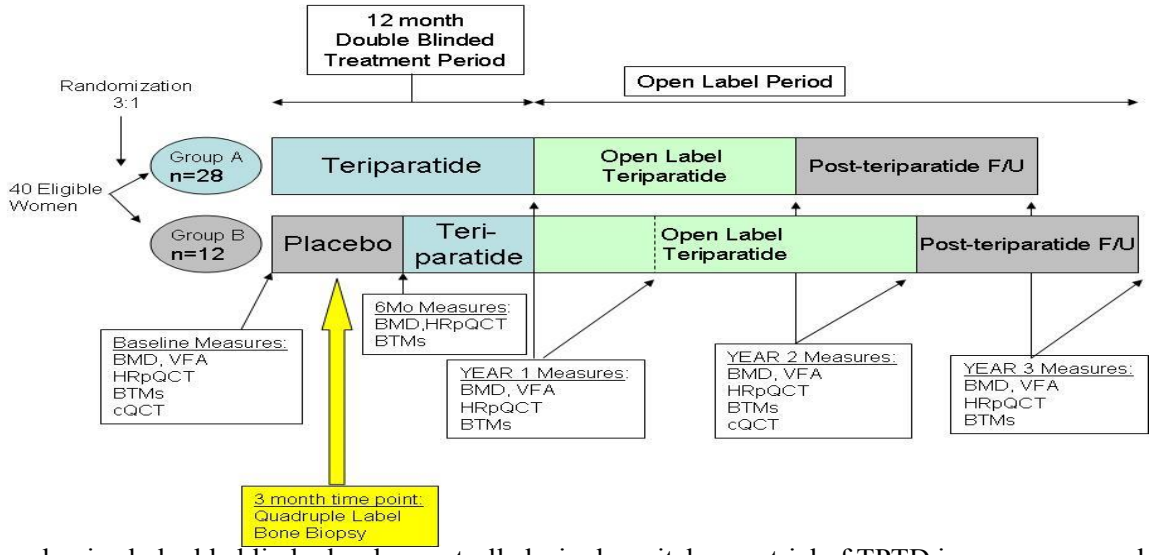
1. One year of observation
2. To leave the study and be treated clinically with an antiresorptive drug to maintain gains in bone density after treatment with TPTD, which is the current clinical standard of care for postmenopausal women and men who have completed two years of TPTD therapy

3. Participation in a new study evaluating anti-resorptive therapy for prevention of bone loss after stopping TPTD. The new study is currently in the design phase and funding phase and precise details are not yet available

All currently enrolled subjects would be re-consented and future participants would sign a new informed consent document with the new study design.

On January 26, 2014, the Research Pharmacy informed the Principal Investigator that there was a mistake in the randomization table for the study. Subjects (n=40) should have been randomized 28:12, active Teriparatide to placebo, for 6 months, followed by a single-switchover design in which all would receive active drug. The randomization code in the table provided to the Research Pharmacy by the Study Statistician was reversed and the subjects were randomized 12:28, active Teriparatide to placebo. To date, 18 patients have been enrolled and randomized. Research Pharmacy has informed us that 12 subjects were randomized to placebo and 6 to active Teriparatide. As 12 subjects have already been randomized to receive placebo first, we will increase enrollment by one subject (total, 41) and generate an adaptive randomization table in which one of the 23 subjects yet to be enrolled will be randomly assigned to placebo and 22 will be randomly assigned to active Teriparatide. This will maintain the number of subjects treated with active drug at 28 and maintain blinding of subjects and study personnel to study assignment.

2. Study Design and Statistical Procedures



The study is a randomized, double blind, placebo-controlled, single switch-over trial of TPTD in premenopausal women with IOP. Forty-one subjects will be assigned to TPTD (Group A; n=28) or placebo (Group B; n=13). At the 6 month timepoint, all subjects will receive TPTD, but blinding of original group assignment will be maintained for an additional 6 months. At the 12 month visit, the blind will be broken and those initially randomized to TPTD (Group A) will continue on study drug for an additional 12 months while those initially randomized to placebo (Group B) will continue for an additional 18 months, so that subjects in both groups complete 24 months of treatment overall. aBMD by DXA and HRpQCT will be measured at baseline and at 6 month intervals. vBMD by cQCT will be performed before randomization and after 24 months of TPTD (Table 1). A quadruple labeled transiliac crest bone biopsy will be performed at 3 months for both Group A and B. Eli Lilly & Company will provide TPTD and placebo but will supply no other funding. After 24 months of treatment in either Group A or B, all women will be offered three choices for follow up: the subjects can A) continue to to be followed for 12 months off TPTD B) choice

to leave the study and be treated clinically using an anti-resorptive medication to maintain gains in bone density after treatment with TPTD, or C) join a new study to maintain gains in bone density after treatment. The new study is currently in the design phase and funding phase and precise details are not yet available.

Statistical Analysis Plan

2.A. Statistical Analysis Plan

Our aims in this protocol are as follows:

Aim 1: To establish the efficacy and safety of 6 months of TPTD versus placebo in premenopausal women with IOP

Aim 2: To determine the effect of 3 months of TPTD on bone remodeling at the tissue level and the extent to which baseline and 3 month bone remodeling predicts response to TPTD in premenopausal women with IOP.

Aim 3: To determine the extent to which 12 and 24 months of TPTD improves areal and volumetric BMD, bone microarchitecture and strength (stiffness) compared to baseline measures in premenopausal women with IOP

Prior to statistical analysis, all outcome and covariate data will be summarized with descriptive statistics, outliers examined, distributions identified and normalizing transformations applied where indicated. All of the above analyses will be based upon the intention-to-treat principle. The missing data mechanism (MCAR, MAR) for all outcomes and covariates will be assessed and, in the event of a non-ignorable mechanism, analyses will subjected to the methods of Diggle and Kenward[39] for continuous measures or Ibrahim and Lipsitz[40] for safety outcomes. Bone turnover markers will be log-transformed prior to analysis. Inferential testing will use a 5% two-tailed type I error rate with no adjustment for multiplicity taken for primary outcome analyses. Secondary efficacy analyses type I error rates will be adjusted by Bonferroni method whereas secondary safety analyses will not. In keeping with the objective of proposed exploratory analyses to generate data patterns consistent or inconsistent with improved bone quality, no adjustment for multiplicity will be taken. No interim efficacy analyses are planned. The statistical analysis plan will be modified to account for the adaptive randomization procedure, which is relevant to Aim 1 only.

AIM 1:

Primary efficacy outcome analysis: Analysis of covariance (ANCOVA) comparison of between-group (treated vs placebo) differences in mean change in LS aBMD (g/cm^2) by DXA from pre-treated baseline to 6 months of assigned treatment with adjustment for the following continuous baseline variables LS aBMD (g/cm^2), age (years) and weight (kg).

Primary safety outcome analysis: Fisher's Exact test of between-group difference in the number of people in each assigned group reporting at least one hypercalcemia or hypercalciuria event in the first 6 months of assigned treatment; followed by Cox proportional hazards model analysis of the between-group difference in the time-to-first hypercalcemia or hypercalciuria event; followed by GEE testing of the between-group difference in the temporal pattern of the repeatedly sampled hypercalcemia or hypercalciuria events in the first 6 months of assigned treatment.

Secondary efficacy outcome analyses: TH, FN and 1/3 Radius aBMD by DXA will analyzed by ANCOVA as described for the primary outcome, above.

Secondary safety outcome analyses: Fisher's Exact test will be used to assess treatment group differences in numbers of people endorsing each symptom reported on the symptom checklist administered at each study visit without adjustment for multiplicity. The GEE test approach proposed for the primary safety

outcome analysis of longitudinal events will be repeated for any symptom reported by >10% of either treatment group.

AIM 2:

Primary analysis: The between-group mean difference in the quad-labeled histomorphometric measured change in Mineralizing Surface (MdPm) and Bone Formation Rate (BFR/BS) at 3 months will be analyzed with ANCOVA with adjustment for the baseline continuous variables of age (years) and weight (kg.). Outcomes will be analyzed separately without adjustment for multiplicity.

Secondary analyses: In the teriparatide-treated group the relationship between baseline MdPm and BFR/BS, and change in MdPm and BFR/BS in the first three months of treatment, and 12 and 24 month change in aBMD of the spine and hip by DXA and vBMD of the spine by cQCT will be assessed with multiple regression analysis. Per annum change in DXA and cQCT outcomes will be separately modeled as a function of baseline MdPm and BFR/BS, baseline level of the DXA or cQCT outcome, age, weight, bone microstructure by microCT of biopsy specimens, and change from baseline in MdPm and BFR/BS during the first three months. Other potential baseline predictors of DXA and cQCT response to teriparatide treatment will be explored with multiple regression to determine whether any clinical or constitutional measures supercede change in MdPm or BFR/BS in predicting bone change.

AIM 3:

Primary efficacy outcome analysis: Analysis by linear mixed models for repeated measures (LMM_R) of the within-group (TPTD) change in LS aBMD (g/cm^2) by DXA from pre-treatment baseline with repeated measures at 12- and 24-months. (This is a growth curve model testing the hypothesis that the temporal trajectory of within-subject change in outcome differs from a random process.) The model estimates the fixed effect of time, random effects for subject, error and the quadratic and cubic values of time entered as random effects, continuous covariates for age and weight at baseline and with an AR(1) covariance structure. The random effects for higher-order factors for time model monotonic and U-shaped components of the growth curve. Model estimated within-subject differences between specific timepoints will be assessed when the fixed effect of time is statistically significant. The LMM_R model will be repeated for LS trabecular vBMD by cQCT after 24 months of teriparatide.

Secondary efficacy outcome analysis: The same LMM_R analysis proposed for Aim 2 primary outcomes will be used for secondary efficacy outcomes of TH, FN and $1/3^{rd}$ RD aBMD by DXA and HRpQCT after 12 and 24 months, and cQCT after 24 months of TPTD. These analyses will also be used to explore the pattern of change in serum BTMs (P1NP and CTx), between baseline and 24 months.

Exploratory analyses will also be conducted to determine whether clinical factors such as age, BMI, body composition, and aspects of the growth hormone axis may predict BMD response to TPTD.

2.B. Power and Sample Size

We have based our power calculations upon the preliminary data generated from our recent pilot study of 22 women with IOP who were treated with teriparatide for 24 months. Our power estimates are based upon 40 women randomized to TPTD or placebo (28:12) with data for analysis, assuming a 10% drop-out and an alpha level of 5%.

AIM 1:

Primary efficacy outcome: For the primary endpoint of between-group difference in LS BMD at 6 months, power calculation assuming the proposed two-group ANCOVA and outcome correlation with baseline covariates of 0.3, we will have >90% power to detect a difference of 3.7 $\pm$ 3.3% in the TPTD-treated vs. 0.8 $\pm$ 2.9% in the placebo-treated group (placebo estimate based on interpolation from our preliminary data at 12 months). The estimated effect size is consistent with an annual TPTD-induced increases of 7.0-13.5% in studies by Arlot et al. in postmenopausal women, Langdahl et al. in premenopausal women with GIOP, and Kurland et al. in male IOP[36].

Primary safety outcome: For our primary safety outcome, the between-group difference in the number of people in each assigned group reporting at least one hypercalcemia or hypercalciuria event, we do not expect to have sufficient power to detect group differences in event rate because of the rarity of TPTD-related safety events observed in our pilot study and reported by others in the literature.
Secondary efficacy outcome: For our secondary efficacy endpoints of between-group differences in TH, FN and 1/3R, our preliminary data suggest that we will not have sufficient power to detect between groups differences in these measures at 6 months, as the increases are less pronounced than at the LS.
Secondary safety outcome: While we will closely examine the safety data, our small sample size provides minimal power to detect any but the most dramatic differences in safety profile between groups.

AIM 2:
Primary efficacy outcomes: For MdPm and BFR/BS after 3 months of TPTD, we base our effect size assumptions on the Lindsay et al[28] estimates of changes from baseline to 1-month of cyclic TPTD treatment (assuming these measures are virtually unchanged over 3 months in the placebo treated group). Lindsay reports cancellous BFR/BS increased from 0.008 ± 0.006 to 0.027 ± 0.018 (a standardized effect size of 1.42) and cancellous MdPm from 1.33 ± 0.95 to 3.78 ± 2.53 after 1 month (a standardized effect size of 1.28). With the proposed sample size, we will have over 90% power to detect difference comparable or larger than the increase in bone formation detected by Lindsay after 1-month of treatment.
Secondary analyses to assess the predictability of DXA and cQCT changes from baseline and 3-month changes in BFR/BS and MdPm: The proposed sample size enables us to detect between 40% to 55% of the variance accounted for in the 12- or 24-month DXA or cQCT change and the baseline to 3-month change in BFR/BS or MdPm (assuming 80% power, 5% alpha and a multiple regression model with up to 3 covariates partialled from both the bone density outcome and the histomorphometric predictor).

AIM 3:
Primary efficacy outcomes: For LS aBMD by DXA after 12 and 24 months of TPTD, we will have >86% power to detect changes from baseline. We based our estimate of LS aBMD at 12 months on our preliminary data, and at 24 months on the data of Graeff et al.[41] who detected a 10.2% increase in aBMD over 24 months. We anticipate that the increase between baseline and 12 months will far exceed the increase from 12 to 24 months, which may not be statistically significant. For trabecular vBMD at the spine by cQCT after 24 months of TPTD, the work of Rehman et al.[32], who detected an increase of 35% in vBMD, suggests that we will have power of >99% to detect within-group changes.
Secondary efficacy outcomes: We will have 99% power to detect within group increases from baseline in TH BMD at 12 and 24 months. This estimate is based upon our preliminary data. We do not have 24 month data; however, published work by Saag et al.[42] and Keaveny et al.[43] suggests that we may not have sufficient power to determine whether TH BMD increases significantly between 12 and 24 months. In addition, we may not have sufficient power to detect significant changes in FN or 1/3R BMD. For HR-pQCT measures, the Bogado study[44] indicates we will have 99% power to detect within group changes in Ct.Th, Tb.N and Tb.Sp.

3. Study Procedures

3.A. Schedule of Visits
Visit 1 (Screening): Women with IOP fulfilling preliminary eligibility requirements (Telephone Questionnaire) will be invited to attend a Screening Visit at CUMC or Creighton. Prior to initiation of any screening procedures, an informed consent discussion will take place. Only after the informed consent (Screening Consent Form) is signed will screening procedures commence.. The visit will be scheduled during days 1-5 of the menstrual cycle to identify women in early menopause (FSH>20 mIU/ml). After a

negative pregnancy test, all will have BMD, VFA and body composition by DXA. Women who fulfill BMD or fracture eligibility criteria will complete a Historical Questionnaire (Appendix 1) on medical and reproductive history (menstrual history, menarchal age, parity, OCP use), risk factors for osteoporosis (eating disorders, alcohol, tobacco, caffeine intake), personal and family history of fractures, current and past medications. The Eating Disorder Examination - Questionnaire (EDE-Q; Appendix 2) will be given to identify women with subclinical eating disorders[45,46]. All will have a standardized physical (weight, height by Harpenden stadiometer) by a physician co-investigator and a Secondary Osteoporosis Evaluations (SOPEval). The following must be normal: blood count, Westergren ESR, C-reactive protein, electrolytes, creatinine, thyroid and liver function tests, uric acid, calcium, phosphate, 25-OHD (>20 ng/dl; those with levels between 21-29 ng/ml will be offered supplementation to achieve levels >30), intact PTH (<65 pg/ml), tissue transglutaminase IgA antibody (tTG; 99% specific and 95% sensitive for celiac disease) and immunoglobulin A (IgA) to exclude celiac disease, 24-h urine for creatinine, calcium (<300mg/gCr) (100-250 mg), free cortisol. Other tests may be performed if less common etiologies are suspected. In some cases, arrangements may be made for some portions of the screening visit procedures (eg laboratory studies) to take place outside of this medical center. In all cases, eligibility will be verified by study physicians.

Visit 2 (Imaging): If the SOPEval is normal, candidates will be invited to proceed with Visit 2. Prior to initiation of any additional study procedures, an informed consent discussion will take place. Only after the informed consent (Study Consent Form) is signed will further research related procedures commence. The study will be described, including the bone biopsy procedure. Participants with fractures will be asked to bring verification (x-rays or radiology reports). They will complete standardized questionnaires to assess current diet and physical activity. We use the validated Block food frequency questionnaire (FFQ; Appendix 3)[47,48] to assess calcium intake. Physical activity is assessed by the modified Baecke questionnaire (Appendix 4)[49-51]. Equivocal VFA results will be evaluated with spine x-rays. Central QCT of the spine (L1 and L2) with additional single slice at L4, and HR-pQCT of the distal radius and tibia will be performed to measure volumetric BMD, body composition (subcutaneous and visceral adiposity), and cortical and Tb microstructure. Serum will be archived at -80^{o}.At this visit, subjects will also receive tetracycline for their first round of antibiotic labeling and instructions with a scheduled dosing according to protocol. Subjects will complete labeling before the randomization visit, where they will receive Forteo and begin treatment.

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Visit 3 (Randomization): During this visit, imaging results will be reviewed with the subjects. Eligible subjects who agree to participate will be randomized to TPTD or placebo (ratio 28:13) through block randomization with randomly varying block sizes of 2, 4 or 6, stratified by whether they are included on the basis of history of fractures or low BMD. Serum/urine will be archived at -80^{o}C for batch analyses of specialized biochemistries. DNA will be obtained from peripheral blood lymphocytes for archival purposes. We will collect blood for the measurement of osteoblasts, or bone building stem cells, in the bloodstream.

Subjects will be provided with calcium (citrate) caplets (Citracal + D; each 315 mg + 250 IU D) and a multivitamin (Centrum) that provides 500 IU of vitamin D daily. Most subjects will be instructed to take 2 Citracal caplets and a multivitamin; the total daily dose of calcium from supplements will be approximately 630 mg and of vitamin D 1000 IU. Subjects with very low dietary calcium intake (<500 mg/d estimated by interview and the FFQ), will be asked to take 3 Citracal caplets, while those with high dietary calcium intakes (>1,000 mg/day) will be asked to take 1 Citracal caplet.

Visits 4-5, 8-13 (Study Evaluations): At each study visit, study coordinators will assess any adverse events that transpired since the last study visit. Patients will be instructed to bring their Forteo journal and pens with them to every visit, which documents their compliance with the study medication. The purpose

of the 1-week and 1-month visits (Visits 4 & 5) is to monitor for compliance and adverse effects. At the 1-week and 1-month visit, we will also obtain fasting serum for serum calcium (safety) and at the 1-Month we will also collect serum for BTMs. These visits may be conducted on site for women who reside close to the study sites or may be a telephone contact and local blood draw for those who live at a distance. The remainder of the study visits to perform imaging studies and/or blood draws and dispense study drug are shown in Tables 1-3. We will perform a single follow-up cQCT scan after 24 months of TPTD treatment to minimize radiation exposure in these women who are of child-bearing age. At Visit 12, subjects will be presented with three options for post-TPTD follow up as described in the study design.

Visit 6 (Pre-Biopsy Clearance and Labeling): Subjects will have a pre-biopsy clearance visit with the surgeon and have safety bloods drawn and processed as per hospital regulations. Subjects will receive their second antibiotic labeling agent, demeclocycline, and accompanying labeling schedule.

Visit 7 (Transiliac Bone Biopsy): Transiliac crest bone biopsy is used to investigate 3-dimensional bone structure and static indices of bone remodeling. Dynamic remodeling indices (e.g., mineralizing surface and bone formation rate) are also assessed with tetracycline labeling techniques. The traditional double label biopsy protocol involves administration of two 3-day courses of tetracycline separated by 12 days. Tetracycline localizes on bone surfaces undergoing active bone formation and permits precise quantification of the rate of bone formation and remodeling. In the quadruple labeling protocol, 2 sets of double tetracycline labels are administered: one set before drug treatment, and a second set after 1-3 months of treatment/placebo; a single biopsy is then performed after the second set of labels (74). Because two different tetracyclines are used that fluoresce in different colors, a single biopsy can be used to assess dynamic indices of bone remodeling before and during drug treatment. This labeling protocol has been previously used by our group to study the osteoanabolic effects of TPTD in postmenopausal women (74) and the effects of hPTH(1-84) in subjects with hypoparathyroidism (75).

Transiliac crest bone biopsy will be performed according to procedures established at CUMC and Creighton. We will be performing the quadruple labeled bone biopsy at the 3 month visit**.** We have a long track record of performing research quality, bone biopsies and have been successful in obtaining bone biopsy specimens in both normal and abnormal cohorts of subjects, including women with IOP.

Table 1: Study Visits		**1** Screen	**2** Imaging	**3** Randomize	**4** 1W	**5** 1M	**6** 2M Labeling	**7** 3M Biopsy	**8** 6M
Consent		x	x						
MD Visit		x	x				**x**[a]		x
Dispense TPTD				x				**x**	x
Telephone Contact[#]					x	x	**x**	**x**	x
Pregnancy Test		x	X	x					x
BMD by DXA		x							x
History & Physical		x							
Questionnaire A & B		x							
Questionnaire C & D			X						
Adverse Events					x	x		**x**	x

Serum FSH		x							
SOPEval [%]		x							
HR-pQCT			X						x
Central QCT			X						
VFA by DXA		x							
Body Composition by DXA		x							
Blood/Serum Archive			x[β]	x[β]		x		**x**	x
24H urine calcium/creatinine		x				x			x[^]
Calciotropic Hormones				x					
Bone Turnover Markers				x		x		**x**	x
Pre-Biopsy Labs							**x**		
Antibiotic Labeling			X				**x**		
Bone Biopsy								**x**	
		[a] **Includes pre-biopsy clearance and consent** [β] Baseline laboratory collection to be split between the 2 collection timepoints # Will occur before the scheduled visit % Includes baseline 24 hour urine ^ Will be collected 1M after 6M treatment with TPTD for safety labs							

Table 2: Study Visits – Group A*	**9** **9M**	**10** 12M	**11** 18M	**12** 24M	**13** 36M
MD Visit		x		x	x
Dispense TPTD		x	X	x	
Telephone Contact[#]	x	x	X	x	x
Pregnancy Test		x	X	x	x
BMD by DXA		x	X	x	x
History & Physical		x		x	x
Adverse Events	x	x	X	x	x
Serum FSH				x	
HR-pQCT		x		x	x
Central QCT				x	
VFA by DXA		x		x	x
Blood/Serum Archive	x	x	X	x	x
Calciotropic Hormones		x		x	x
Bone Turnover Markers		x	X	x	x
	* Only for treatment group assigned immediately to active treatment (Group A) # Will occur before the scheduled visit				

Table 3: Study Visits – Group B**	**9 9M**	**9** 12M	**10** 18 M	**11** 24 M	**12** 30 M	**13** 42 M
MD Visit		x		x		X
Dispense TPTD		x	x	x		
Telephone Contact[#]	X	x	x	x	X	X
Pregnancy Test		x	x	x	X	X
BMD by DXA		x	x	x	X	X
History & Physical		x		x		X
Adverse Events	x	x	x	x	X	X
Serum FSH					X	
HR-pQCT			x		X	X
Central QCT					X	
VFA by DXA		x		x		X
Blood/Serum Archive	x	x	x	x	X	X
Calciotropic Hormones		x		x		X
Bone Turnover Markers		x	x	x	X	X
	** Only for treatment group that started with 6 months of placebo injections (Group B) # Will occur before the scheduled visit					

For the sub-study: This sub-study involves only one visit that can be done at the same time as a visit completed for the main study. Four blood draws will be performed. These bloods will be collected while subject is fasting. The first blood draw will be collected right before the subject completes the Forteo injection. These will be considered the baseline bloods. The remainder 3 blood draws will be collected 30 minutes after injection of Forteo, 60 minutes after Forteo injection and 4 hours after Forteo injection. Samples will be stored for measurement of drug (Forteo: PTH1-34) and drug effects (calcium).

3.B Study Procedures

1. BMD by DXA: Areal BMD (aBMD) of the LS (L1-4), proximal femur and non-dominant forearm will be measured at CUMC on Hologic QDR 4500 densitometers (Hologic, Inc., Waltham, MA). Dedicated technologists, certified by the International Society of Clinical Densitometry, with long-term research experience perform all scans. Phantoms are scanned daily to check for detector drift; the results are appended to a quality control (QC) database. Results are downloaded to specific project databases. The effective dose for BMD by DXA is7.45 μSv.

2. Body Composition by DXA: Total fat mass, lean mass, and percent fat mass will be measured by DXA. The effective dose for whole body DXA is 5.2 mrem. Our precision is 1%.

3. Vertebral Fracture Assessment (VFA) by DXA: Visual semiquantitative identification of vertebral fractures is obtained from images acquired by fan-bean DXA scanners. VFA demonstrates good agreement with conventional radiographs (96.3%, k=0.79) in classifying vertebrae as normal or deformed. With its low radiation and good precision, VFA is useful to identify subjects with and without vertebral fractures. The total effective radiation dose associated with each VFA 5.2μSv.

4. High Resolution Peripheral Quantitative Computed Tomography (HR-pQCT): HR-pQCT is performed on the XtremeCT (Scanco Medical AG, Switzerland). The nondominant distal radius and tibia are immobilized in a carbon fiber shell (158-160). The region of interest is defined on a scout film by manual placement of a reference line at the endplate of the radius or tibia; the first slice is 9.5 mm and 22.5 mm proximal to the reference line at the radius and tibia respectively. A stack of 110 parallel CT slices is acquired at the distal end of both sites using an effective energy of 40 keV, slice thickness of 82

μm, image matrix size 1024x1024, nominal voxel size of 82 μm. This machine provides a 3D image of 9 mm in the axial direction. HR-pQCT provides microstructural information (cortical and trabecular density, cortical thickness, trabecular number, thickness and separation) previously obtainable only by an invasive bone biopsy. We are one of only 5 US medical centers with this new technology. For HRpQCT of the forearm and leg, the estimated effective whole body dose is below 5 μSv per scan, since only a very small fraction of the distal forearm or leg is irradiated.

5. Volumetric BMD by Central QCT: Volumetric QCT acquisitions of the L1-L2 vertebrae (80 kVp, 140 mAs, 2.5 mm slice thickness, pitch=1.2, standard reconstruction algorithm, 3-Bar Image Analysis QCT Calibration Phantom (Image Analysis, Columbia, KY) will be carried out on a Siemens Biograph 40 Slice CT Scanner (Siemens Medical Solutions, Malvern, PA), located within CUMC's Kreitchman PET/CT Center. Scan data are archived to CD and forwarded to a central analysis site (UC San Francisco, Dept. of Radiology) for scan quality assurance and analysis. Spine CT images are analyzed with image analysis software developed by our collaborator and consultant, Thomas Lang, Ph.D. L1-L2 measures analyzed by this software include vBMD of an integral compartment containing the vertebral body and posterior elements (viBMD), the areal BMD of this region obtained by computing its bone mineral content and dividing by the projected area in the AP plane (QCTaBMD), and the vBMD of a region containing almost all of the trabecular bone in the vertebral centrum (vtBMD). BMD data obtained on each scanner are converted to the calibration-phantom equivalent BMD. To ensure comparability of data obtained on different CT scanners used at CUMC, CT data are cross-calibrated using the Image Analysis Torso Quality Control phantom (Image Analysis, Columbia, KY) which is scanned multiple times on each system. Total effective radiation dose from a central QCT scan of the spine is estimated at 470 μSv which is equivalent to approximately 2-3 months of background radiation (assumed to be 3 mSv/year).

6. Body composition by CT: At the time that L1-L2 cQCT measures are acquired, as above, one additional axial image slice (10mm thick) will be obtained at the mid L4 vertebra level[77]. Based upon this image, the cross-sectional areas of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) in cm^2 will be calculated by the method of Zhao et al [54]. The additional radiation exposure from the single slice is estimated to be 10% of the exposure for the L1-L2 scan above (approximately 5μSv).

7. Spine Radiographs: Lateral thoracic and lumbar spine radiographs for diagnosis of prevalent or incident vertebral fractures, performed using the protocol used in the Study of Osteoporotic Fractures (SOF) [55], will be used in subjects for whom VFA diagnosis of fractures is ambiguous. Total critical organ absorbed dose from a lateral thoracic and lumbar spine radiograph is equivalent to about 350 mrem. Our skeletal radiologist, Ronald Staron, M.D., evaluates and reads these x-rays.

8. Biochemical Assays: All blood samples will be collected fasting in the morning. General tests (CBC, serum calcium, phosphate, albumin, renal and liver function tests, urine calcium and creatinine) will be run when collected by standard methods. Serum for PTH, 25-OHD, $1,25(OH)_2D$, osteocalcin, BAP, P1NP, CTx, IGF-I, IGFBPs, leptin, adiponectin, insulin, glucose, IL-6, homocysteine, c-reactive protein (CRP), lipid studies, E2, testosterone, SHBG, OPG, RANKL will be aliquoted, frozen immediately and stored at -80^o. Specimens will be shipped frozen from the CORC to Columbia. Additional serum/urine will be archived for measurement of BTMs and mineral metabolites that may become available in future. Blood for DNA will be obtained from peripheral blood lymphocytes for archival purposes. We intend to isolate and store these samples for future genetic studies that may identify a polymorphism linked to one of our phenotypes, or identify a new candidate gene polymorphism in our study population. Blood for osteoblasts, which are bone-building stem cells, found in the bloodstream, will be collected. These will be processed and stored frozen at -80°C. All assays are currently in place either in the CUMC Bone Marker Laboratory within the Division of Endocrinology, under the direction of Serge Cremers, PhD., PharmD or

the Core Laboratory of the Irving Institute for Clinical and Translational Research (CUMC CTSA). Lipid particle size analysis will be conducted at Liposcience, Inc.

9. Bone Biopsy of Iliac Crest: Transiliac crest bone biopsy will be performed according to procedures established at CPMC and CORC. Participants will receive instructions and medications for tetracycline and demeclocycline "quadruple labeling" at the beginning of the study and one month prior to second label. Transiliac crest bone biopsy will be performed according to standard procedures established here at CUMC and Creighton University under the direction of Drs. Shane and Recker, who both have long track records of performing successful research quality bone biopsies. Bone biopsies will be performed by Dr. Shane, Dr. Stein or Dr. Nickolas in the Milstein Operating Rooms at CUMC. The biopsy sample will be placed in a 30 ml liquid scintillation vial containing 70% ethanol and shipped to Dr. Ralph Müller's laboratory for microCT and FEA. Next, the specimens will be shipped to Dr. David Dempster's laboratory (Helen Hayes Hospital, West Haverstraw, NY) for embedding and analysis.

4. Study Drugs or Devices

Teriparatide has been FDA approved for the treatment of osteoporosis since November 2002. The pen delivery device will be fully coded and ready for distribution by our research pharmacy. Two identical sets of pens will contain placebo (vehicle alone) or 20 mcg of teriparatide. Drug will be stored in a refrigerator in the research pharmacy until it is dispensed. Subjects will be instructed to refrigerate the medication at home during their pen training.

The study drug will be packaged in a pre-filled pen delivery device (20 mcg or placebo in 3 ml) in such a manner as to make active and placebo TPTD indistinguishable. Each pen will be labeled with the subject identifier and the 24-hr telephone number of the research pharmacist who will retain information of treatment allocation in the event that unblinding becomes necessary. All other study related items and documents are only identified with the subject identifier. All subjects will be trained to self-administer agent (drug or placebo) by our research nurse. All medication will be dispensed by the research pharmacy of the Office of Clinical Trials at Columbia University.

5. Study Instruments

Subjects will complete the following standardized questionnaires as part of this protocol.

1. Historical Questionnaire on medical and reproductive history (menstrual history, menarchal age, parity, OCP use), risk factors for osteoporosis (eating disorders, alcohol, tobacco, caffeine intake), personal and family history of fractures, current and past medications.
2. Dietary Rapid Calcium Assessment to assess calcium intake
3. The Eating Disorder Examination Questionnaire (EDE-Q) to screen out subjects with a current eating disorder
4. Block Food Frequency Questionnaire (FFQ) to assess dietary habits
5. Modified Baecke Questionnaire to assess physical activity
6. Phone Screening Questionnaire

Questionnaires 2-4 are all validated, standardized instruments. These questionnaires are all attached in the RASCAL system.

6. STUDY SUBJECTS

Inclusion Criteria:

- Premenopausal women, aged 20-48, with regular menses and no historical or biochemical secondary cause of osteoporosis; the lower age limit is to ensure epiphyses are fused, the upper to make it less likely that women will enter menopause during the study. All subjects under age 25 will be screened prior to drug administration to rule out open epiphyseal plates.

- Documented adult fractures judged to be low-trauma (trauma equivalent to a fall from a standing height or less) and/or T $\leq$ -2.5 or Z score $\leq$-2.0 at the LS, FN or TH. Inclusion criteria vary slightly based on age category:
    - Premenopausal women ages 20-35 years must have at least one major osteoporotic fracture (excluding fractures of fingers, toes and face) AND low BMD defined as a T-score or Z-score $\leq$ -1.5.
    - Premenopausal women above the age of 35 years should have a history of fracture AND/OR low BMD defined as Z-score < -2.0. Women above age 35 may also be enrolled on the basis on low BMD alone, without presence of prior low trauma fracture.
- Must be willing to use effective contraception throughout the period of study drug administration

Exclusion Criteria:

- History of any condition that increases the risk of osteosarcoma (Paget's disease, skeletal irradiation)
- Early follicular phase serum FSH>20 mIU/ml (to exclude perimenopausal women)
- Disorders of mineral metabolism: $1^{o}/2^{o}$ hyperparathyroidism, osteomalacia, osteogenesis imperfecta (OI) or Ehlers Danlos (ED). Subjects will not routinely undergo genetic testing for OI or ED as part of their screening evaluation. However, each subject will have a detailed medical and family history and a complete physical examination by one of the physician investigators. Women with historical features or physical examination findings suggestive of OI or ED will be referred for genetic evaluation. If the genetic evaluation is positive for OI or ED, the subject will be excluded from participation.
- Suspicion of osteomalacia (elevated alk phos, worsening bone pain with weight bearing, or bone tenderness)
- Vitamin D deficiency (serum 25-OHD$^{<}$20 ng/ml). Women with levels of 10-20 ng/ml will be eligible after treatment with vitamin D has resulted in levels $\geq$20 ng/ml.
- Pregnancy within the last 3 months if there was no lactation or lactation within past 6 months
- Prolonged amenorrhea ($\geq$ 6 months) during reproductive years (except pregnancy or lactation)
- Prior eating disorder (hypothalamic or exercise induced amenorrhea now resolved may be acceptable if symptoms occurred at age >20 years, for <1year, >5 years ago)
- Malignancy, except cured basal or squamous cell skin carcinoma
- Endocrinopathy: new onset untreated hyperthyroidism, hypothyroidism, Cushing's syndrome, prolactinoma
- Renal insufficiency (serum creatinine above upper limit of female normal range)
- Liver disease (AST, ALT, bilirubin, total alkaline phosphatase activity above upper normal limit)
- Intestinal disorders (celiac disease, pancreatic insufficiency, inflammatory bowel disease)
  IBD: only Crohn's Disease or Ulcerative Colitis are exclusions
- History/current GCs, anticonvulsants, anticoagulants, methotrexate, depot progesterone, GnRH agonists
- Oral glucocorticoid use (subject will not be excluded if used dose equivalent to less than prednisone 5 mg for <3 months). Inhaled steroid exposure will require assessment of dose used.
- Current anticoagulant use (past use of warfarin (Coumadin) or low molecular weight heparin is not an exclusion)
- Depo Provera use (subjects will not be excluded if used at age>20, >5 years ago)
- Drugs for osteoporosis (raloxifene, bisphosphonates, denosumab, calcitonin, TPTD). Subjects who discontinue these medications will be eligible 3 months after stopping raloxifene or calcitonin, 12 months after stopping alendronate, risedronate, ibandronate, or pamidronate and 18 months after stopping denosumab. Subjects with prior use of zoledronate may be eligible if received only one dose >4 years ago. Total bisphosphonate exposure must be $\leq$ 1 year. Subjects who have taken TPTD in the past will not be eligible unless used for <3 months, > 2 years ago.

7. RECRUITMENT

Subjects from CUMC will be recruited from previously enrolled and newly recruited subjects. Recruitment to studies of uncommon diseases is always challenging. Although recruitment of cases to the original R01 grant (AAAA9245) was slow for the first 2 years, we ultimately enrolled 64 subjects with IOP. In addition, we were able to recruit 22 women to the pilot study of TPTD in Premenopausal Women with IOP in 12 months. Our study teams have developed ongoing relationships with these patients that will be useful in recruitment. We anticipate that some of the subjects in protocol AAAF2251 will come directly from protocol AAAA9245, as, in our experience, many women with IOP are anxious to pursue treatment options for their condition.

We recruit subjects locally, nationally and internationally. Locally, we recruit patients referred to the Metabolic Bone Disease Unit at CUMC in New York. We post flyers and speak at inter-departmental and inter-institutional conferences, particularly to Orthopedics and Obstetrics & Gynecology departments. We speak at national and international conferences (ISCD, NOF, ECTS, ASBMR, TES). Dr. Shane recently conducted the first ASBMR Webinar on premenopausal osteoporosis, which was attended by >200 individuals. We send biannual email reminders to physicians from surrounding states of both centers who care for patients with osteoporosis and also to our clinical colleagues in ASBMR. The study will be posted on CUMC, NOF, NIH, and clinicaltrials.gov. A large source of referrals is patients themselves.

When a patient is referred to our center, we will conduct a brief phone screening to ascertain whether the subject may be appropriate for the study. Prior to enrollment, a study investigator or research coordinator will review the study at length with the subject during the informed consent process.

8. INFORMED CONSENT PROCESS

Written consent will always be obtained according to appropriate Informed Consent forms that will be reviewed and approved by the institutional review board of the Columbia University Medical Center. Potential participants are assured that participation is voluntary and that refusal to participate will not influence their care. Statements to this effect will be included in all Informed Consent forms, which will be signed by the investigator or coordinator obtaining consent and by the subject. All investigators and coordinators have completed courses in Good Clinical Practices and HIPAA compliance. Written informed consent will be obtained for every subject by the investigators after an explanation of the purpose, risks and benefits of the study. Confidentiality will be guarded with the use of computers that are password protected and storing questionnaires with sensitive information within a locked file. All subjects will be provided with instructions on how to contact the investigative team if any problems or concerns arise.

The informed consent process will be conducted by a study investigator or research coordinator prior to initiation of study-related procedures. Subjects will have an opportunity to asked questions prior to signing the form, and all participants will receive a copy of the signed consent form for their records.

9. CONFIDENTIALITY

Confidentiality of patient data in this project will be ensured. Personal Identifying Health Information (PHI) of participants will be kept only in secure files accessible to the PI, investigators and project coordinators. Data will be recorded on case report forms on which the only identifier is a research ID code. Only the PI and project coordinator have access to the link between the research ID code and PHI. No names or identifying information will be included in research reports. Subjects' names will not appear on questionnaires. All computers housing research data have passwords and timed screen savers requiring a password for access. Through these safeguards, the confidentiality of the data will be ensured.

Information obtained in the setting in this study may be made available to the following entities:

- The investigator, study staff and other health professionals who may be evaluating the study
- Columbia University
- New York Presbyterian Hospital
- Authorized representatives of the Food and Drug Administration ('FDA'), the Office of Human Research Protections ('OHRP') or other government regulatory agencies
- Applicable Institutional Review Boards ('IRBs') that independently review the study to assure adequate protection of research participants, as required by federal regulations.

The investigator, regulatory authorities, IRB and study sponsor may keep the research records indefinitely. If the results of the study are published or presented at a medical or scientific meeting, subjects will not be identified.

10. PRIVACY PROTECTIONS

We will take all necessary steps to safeguard each participant's expectation that the information they offer will be held in confidence. These protections will apply to all research related data collection and procedures, as well as to all forums

Only a select group of study personnel will have access to patient study files. We are fully committed to safeguarding an individual's expectation that the information they offer will be held in confidence. All subjects will sign a HIPAA form in addition to the informed consent document to prevent inappropriate use or any disclosure of individuals' health information and to require any organizations which use health information to protect that information and the systems which store, transmit, and process it. The subject has the right to revoke the authorization for us to access her health information at any time, as is stated in the HIPAA form that each subject will sign prior to participation.

Our safety reporting responsibilities require the investigator to report any adverse events to the IRB, the FDA and Eli Lilly, who is providing us with the study drug. These reports will include only a study ID, and will not divulge the participant's identity.

11. POTENTIAL RISKS

The risks of this study are related to the venipuncture, radiation exposure and the study medication, teriparatide.

1) Teriparatide

a. Teratogenicity: In contrast to bisphosphonates, TPTD does not accumulate in the skeleton. Therefore, teratogenic effects, if any, would essentially be limited to the period of administration. Thus, it is a more attractive choice for treating osteoporosis in women of childbearing age, as there would be no potential for subsequent pregnancies to be affected by residual drug. All participants will be required to use effective contraception during the study.

b. Osteosarcoma: Rats exposed to TPTD, in amounts 3-58 fold higher than the human dose for the equivalent of 75 human years (18-24 rat months), develop osteosarcoma in a dose related manner. Therefore, the FDA approved TPTD for therapy of osteoporosis with a "black box" warning and recommended a 2-year limit on duration of treatment. It is highly likely that this toxicity as particular to the rat. There are marked differences in skeletal physiology between rodents and primates. The rat skeleton grows throughout most of their lives[56] and shows very little evidence for remodeling. In contrast, humans typically cease longitudinal growth by 15-20 years of age[57] and the adult human skeleton is characterized by remodeling rather than growth. Perhaps because of these differences, the anabolic response of the rat skeleton to daily PTH treatment is far greater in rats[58] than in humans[59]. Most recently, in a second toxicity study in rats, a "no effect" dose was defined that was larger than any human being will experience[60]. Finally, there was no evidence of any carcinogenic toxicity when the non-human

primate macaque was treated with the same toxicity protocol[61]. To date, two cases of osteosarcoma have been reported in among almost 430,000 patients treated with TPTD[62-64]; this is approximately the same incidence as the 1.7 patients expected to develop osteosarcoma by chance alone, given an expected incidence of 4-5 per million. An additional case recently reported in abstract form, had osteosarcoma before TPTD was initiated[65]. Moreover, the pathology of the first case was controversial and the second case developed in a man who had received pelvic radiation for prostate cancer and the cancer developed within the field of radiation, rather than in the long bones, as is typical of sporadic osteosarcoma[64]. Among the millions of individuals with hyperparathyroidism who are exposed to chronically elevated levels of PTH, there are only rare reports of osteosarcoma, most of which have not been well-documented[66]. There were no reports of osteogenic sarcoma among the participants in any of the clinical trials with PTH, amounting to over 2500 patients. In the largest clinical trial with 1637 subjects, there was no increase in cancer incidence between subjects receiving TPTD and placebo and no woman developed an osteosarcoma[28]. Given all these considerations, it appears that, in general, PTH is safe in humans and that TPTD will be a safe treatment for premenopausal women with IOP. Nevertheless, it is important that subjects in this study are informed of the rat toxicity data and the case reports. Consistent with FDA guidelines, no patient will receive active drug for more than 2 years. In addition, the dynamic histomorphometry measurements we will have will offer an extra measure of safety parameters. We plan to minimize the already small risk by excluding adolescents who may not have fused epiphyses and women with a history of skeletal radiation.

c. Hypercalcemia, Hyperuricemia and Hypercalciuria: Hypercalcemia and mild increases in serum uric acid are known side effects of PTH, although not very common at the FDA-approved 20 mcg/day dose that we will use. A post-hoc analysis of two prospective randomized clinical trials involving 1,637 postmenopausal women and 2,437 men found that urinary calcium excretion increases by an average of 32 mg/d on the 20 mcg dose of TPTD[67]. Dr. Shonni Silverberg, the Study Monitor, will monitor pre-dose serum calcium and uric acid and urinary calcium excretion at 1 to 6-month intervals to determine the incidence of these abnormalities in our study participants. We will exclude subjects with hypercalcemia (fasting serum calcium >10.2 mg/dl) and hypercalciuria (>300 mg/g creatinine) at baseline.

For subjects in the placebo group during months 0-6, there may be a risk of bone loss. However, Peris et al. reported a retrospective analysis of 16 women with IOP, managed with calcium, vitamin D and increased physical activity[68] They documented small increases in BMD and no fractures over an average 3 years of observation, supporting the safety of a placebo-controlled design. We have longitudinal BMD data in 18 women with IOP followed on calcium (1000-1500 mg/day) and vitamin D (800-1000 IU/day) for an average of 4 years. LS BMD increased by 0.8 $\pm$ 2.9%, while there were slight decreases at the FN (-1.2 $\pm$ 5.3%), TH (-0.5 $\pm$ 3.4%) and 1/3 Radius (-2.4 $\pm$ 2.8%). None of the decreases were statistically significant. Thus, we do not expect major declines in BMD in the women randomized to placebo for the first 6 months and in any case, all subjects will receive teriparatide after the first 6 months.

2) Radiation

Radiation exposure (effective dose) for DXA of the spine, hip and forearm with the Hologic QDR4500 is 7.45 µSv, for VFA 5.2 µSvand for Body Composition is 5.2µSv. This is about the amount the average person receives from background radiation in 19 days. For HRpQCT of the forearm and leg, the estimated effective whole body dose is below 5 µSv per scan, since only a very small fraction of the distal forearm or leg is irradiated. Radiation exposure from a central QCT scan of the spine and additional slice for body composition is about475 µSv, which is equivalent to approximately 3 months of background radiation. In subjects where VFA diagnosis of fractures is ambiguous, subjects will be asked to have lateral thoracic and lumbar spine radiographs to assess presence of a vertebral compression fracture. This amounts to the equivalent of an extra 12 months of background radiation. We anticipate that the need for this additional procedure will be necessary in less than 10% of subjects.

For purposes of comparison, this amount of radiation exposure is similar to that associated with many other x-ray procedures: 45 mrem for a mammogram, 1300-1800 mrem for a standard abdominal/pelvic or chest CT scan, 6 mrem for a round-trip transcontinental plane flight and 240-360 mrem natural background radiation in a year. Expressed as equivalencies to background radiation, a standard mammogram, often obtained annually, is associated with radiation exposure equivalent to approximately 2 to 3 months of natural background radiation. A standard abdominal or chest CT scan is associated with radiation exposure equivalent to approximately 24 to 60 months of natural background radiation. Thus, the maximum amount of radiation that would be received by participation in this study (<600 mrem) is less than that from a standard CT scan of the chest or abdomen. We will counsel all study subjects about the total amount of radiation that they will receive as a result of participation as part of Informed Consent procedures of that particular study. In addition, they will be counseled that radiation exposure is cumulative throughout life and any additional exposure should be considered carefully.

Incidental findings: Upon finding of an incidental finding (IF), the clinical readers have been instructed to inform the research team of the study regarding the subject. The subject will be informed of the IF in accordance with timing related to the Class A or Class B severity by the PI of the study. Imaging results will be sent to subject's primary care provider as requested.

3) Venipuncture
The risks of venipuncture for blood drawing include pain, bleeding, bruising, and a remote possibility of infection or inflammation at the site. Additionally, there is a possible risk of syncope in individuals who are prone to vasovagal responses. To minimize these risks, trained phlebotomists who follow proper technique perform all venipunctures.

12. DATA AND SAFETY MONITORING

A Data and Safety Monitoring Board will be established. The DSMB will monitor subject accrual, ethical conduct of research, as well as oversee adverse events and any unforeseen consequences in the study population. The DSMB that will be convened will include three members who will be independent of Columbia University College of Physicians & Surgeons and Creighton University. Among them will be an endocrinologist with expertise in osteoporosis, a physician outside of the field of metabolic bone diseases, and a statistician. The DSMB will be independent of all study personnel, and will sign a conflict of interest form to that effect. It will meet semi-annually by conference call and as necessary in case of complications or issues. The DSMB may recommend any steps necessary to protect the participants.
Interim Analysis: No efficacy interim analysis is planned. The proposed recruitment of a modest number of subjects in each group, with the anticipated recruitment schedule, diminishes the need for an interim efficacy analysis. However, this decision will be reviewed at the first meeting of the DSMB. Performance data will be evaluated. The first interim look at performance will occur when the initial 20 participants have completed the 6-month follow-up visit; thereafter interim reviews will occur at 6-month intervals.
Stopping Rules: Stopping rules will be invoked if new information emerges making the questions in this proposal moot or new information provides evidence suggesting that the use of TPTD in premenopausal women with IOP is contraindicated.
Protocol Modifications: Modifications will not be undertaken without notification of the IRB, the DSMB and the FDA Program Officer for the grant.
Registry: All subjects enrolled on our protocol will be counseled on enrollment in the FORTEO Patient Registry (http://www.forteoregistry.rti.org/). We are supportive of this program as a way to learn more about the long-term safety of using this medication.
Reporting: All adverse events will be reported according to the guidelines set forth by the FDA and applicable IRBs. We commit to follow the FDA reporting requirements set forth in the Code of Federal Regulations Title 21, Section 312.32, which is summarized below.

The sponsor shall notify FDA and all participating investigators in a written IND safety report of:
(A) Any adverse experience associated with the use of the drug that is both serious and unexpected; or
(B) Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity. Each notification shall be made as soon as possible and in no event later than *15 calendar days* after the sponsor's initial receipt of the information. Each written notification may be submitted on FDA Form 3500A or in a narrative format and shall bear prominent identification of its contents

The sponsor shall also notify FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but in no event later than *7 calendar days* after the sponsor's initial receipt of the information. Each telephone call or facsimile transmission to FDA shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND.

The Principal Investigator will ensure that the FDA is informed of actions, if any, taken by the IRB as a result of its continuing review and summary reports will be submitted annually to the FDA. All adverse events that meet the criteria of Columbia University (CU) IRB's reporting policy are reportable to the IRB (link to policy is included below). The CU IRB requires reporting of all unanticipated problems considered to be unexpected, related or possibly related to participation in the research, and that suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized. The timeliness of this report will depend on whether the event is considered to be serious and whether it occurred at an internal or external site. Annual reports will be submitted to the IRB documenting all adverse events and unanticipated problems. Individual serious adverse events will be reported to the IRB and DSMB within 1 week. The PI will forward the report to the IRB and FDA devoid of patient-specific information.

Columbia University IRB Reporting Policy:
http://www.cumc.columbia.edu/dept/irb/policies/documents/UnanticipatedProblemsPolicy.FINALVERSION.012408.pdf)

Creighton University IRB Reporting Policy
http://www.creighton.edu/fileadmin/user/ResearchCompliance/IRB/Policies_and_Procedures/120_Unanticipated_Problems_Involving_Risks_to_Participants_or_Others.pdf

13. POTENTIAL BENEFITS
The IOP subjects may or may not benefit directly from this study. If patients respond to the medication they receive, they will benefit by improving their bone architecture, bone strength, and resistance to fractures.

On a wider scale, the information gained from this research project may apply to all women who have idiopathic osteoporosis and may directly impact upon the future treatment of this puzzling disorder.

14. ALTERNATIVES
The alternative is not to participate in this trial. If a subject decides to withdraw, she will be counseled about other, alternative osteoporosis treatment options. Alternate therapies include, but are not limited to, Alendronate (Fosamax), Risendronate (Actonel), Ibandronate (Boniva), Zometa (Reclast), Denosumab (Prolia).

15. RESEARCH AT EXTERNAL SITES

Research for this protocol will be conducted at Columbia University Medical Center in NY, NY and at Creighton University Medical Center in Omaha, NE. The research team at Creighton University will be responsible for securing IRB approval for all research activities conducted at their site related to this protocol. We will maintain current versions of all IRB approvals and approved documents (ie – consent forms, etc) at our site and submit any changes promptly to the CUMC IRB. Our plan for data and safety monitoring will include monitoring activities and outcomes at both study sites.

16. COLUMBIA AS LEAD INSTITUTION

Columbia University will be considered the lead institution in this protocol. There will be one other site, Creighton University. As stated in the prior section, we will commit to the following: 1) obtain and maintain IRB approval at the Creighton site; 2) ensure that the Creighton site follows consent procedures and utilizes consent documents approved by their IRB (if the designated IRB is not the CU IRB, then the IRB-approved consent document must be similar to the CU IRB-approved consent document with regards the content and style of the document).

Creighton University's Federal-Wide Assurance # is FWA00001078.

17. Sponsor Responsibilities

Study compliance and subject safety will be monitored periodically by the sponsor-investigator, Dr. Elizabeth Shane. The task of overseeing subject safety will be the joint responsibility of both the DSMB as well as the task of the study investigators. Adverse events and/or unanticipated problems will be reported to the Columbia IRB in accordance with their policy and to the FDA in accordance with their reporting guidelines (see Section 12.0 for more detailed information). Study compliance and assurance that the study is conducted in accordance with the protocol will be facilitated by a protocol and operations manual developed by the investigator. Participating research personnel will be instructed in proper forms completion and electronic data entry procedures, as it is applicable to their study role. Adherence with the study protocol and recruitment goals will be monitored by the sponsor on an ongoing basis, with monthly conference calls made to participating sites (Creighton University). Upon identification of incomplete reports or missing data, this information will be obtained from the study site in writing.

It is the responsibility of the sponsor-investigator to submit all amendments, IND safety reports and annual reports to the FDA in compliance with the relevant institution's policies for reporting. Amendments to the protocol must be approved by the IRB prior to the implementation of any changes to the protocol or consent forms, including, but not limited to, study questionnaires, procedures, and recruitment methods.

Records and documentation pertaining to the protocol will be kept in the protocol regulatory binder and online through the Columbia RASCAL system. Subject specific records will be stored in a password protected database or in a locked cabinet to ensure privacy and confidentiality, as is detailed in Sections 9.0 and 10.0. Data entry will be ongoing throughout the course of the protocol so that interval reports to the investigator, IRB and other regulatory bodies are readily accessible.

18. Timeline:

9/16/11 – 1/31/12	Define and refine study operations prior to funding
2/1/12 – 2/29/12	Begin recruitment
1/31/14	Complete recruitment
7/31/14	Last subject completes randomized phase and bone biopsy
8/1/14 - 9/1/14	Data checking, analysis and manuscript preparation for Aim 1 and Aim 2 (primary analysis) outcomes
3/15/15	Apply for no cost extension
7/31/16	Last subject completes drug treatment phase

8/1/16 – 9/1/16 Data checking, analysis and manuscript preparation for Aim 2 (secondary analyses) and Aim 3

19. Literature Cited.

1. Osteoporosis prevention, diagnosis, and therapy. Jama 2001;285:785-95.
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