

Clinical Research Protocol

NOVEL COMBINATION THERAPY FOR OSTEOPOROSIS IN MEN

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CHANGE LOG

VERSION	DATE	ACTION
1.0	08/03/2018	PROTOCOL VERSION 1.0 SUBMITTED
2.0	10/08/2018	PROTOCOL VERSION 2.0 SUBMITTED
3.0	03/18/2019	PROTOCOL VERSION 3.0 SUBMITTED
4.0	05/14/2019	PROTOCOL VERSION 4.0 SUBMITTED
5.0	04/27/2020	PROTOCOL VERSION 5.0 SUBMITTED
6.0	05/03/2021	PROTOCOL VERSION 6.0 SUBMITTED
7.0	10/06/2021	PROTOCOL VERSION 7.0 SUBMITTED
8.0	01/19/2022	PROTOCOL VERSION 8.0 SUBMITTED
9.0	09/19/2022	PROTOCOL VERSION 9.0 SUBMITTED

CLINICAL RESEARCH PROTOCOL

Protocol Number:	19-27836
Version Date:	09-19-2022
IND Number:	134279
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Approval:

09-19-2022

PI or Sponsor Signature (Name and Title)

Date

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PROTOCOL AGREEMENT

I have read the protocol specified below. In my formal capacity as Investigator, my duties include ensuring the safety of the study subjects enrolled under my supervision and providing the University of California, San Francisco Institutional Review Board (IRB) and the San Francisco Veterans Affairs Health Care System Research Office with complete and timely information, as outlined in the protocol. It is understood that all information pertaining to the study will be held strictly confidential and that this confidentiality requirement applies to all study staff at this site. Furthermore, on behalf of the study staff and myself, I agree to maintain the procedures required to carry out the study in accordance with accepted GCP principles and to abide by the terms of this protocol.

Protocol Number: 19-27836

Protocol Title: Novel Combination Therapy for Osteoporosis in Men

Version Date: 10-06-2021

Dolores Shoback MD

09-19-2022

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LIST OF ABBREVIATIONS

1,25(OH)₂D	1,25-dihydroxyvitamin D
25(OH)D	25-hydroxyvitamin D
AE	Adverse event
BMD	Bone mineral density
BTM	Bone turnover marker
BMI	Body mass index
BSAP	Bone specific alkaline phosphatase
Ca	Calcium
[Ca]_e	Extracellular calcium concentration
CaSR	Extracellular Ca-sensing receptor
CBC	Complete blood count
CFR	Code of Federal Regulations
Cr	Creatinine
CRC	Clinical Research Center
CKD	Chronic kidney disease
cKO	Conditional knockout
Col1	Type 1 collagen
CRC	Clinical research center
CRF	Case report form
CRS	Clinical Research Services
CSRD	Clinical Research Services Research and Development
Ct	Cortical
CtTV	Cortical tissue volume
CtBV	Cortical bone volume
CtTh	Cortical thickness
CTSI	Clinical and Translational Science Institute
CTx	C-telopeptide
DHHS	Department of Health and Human Services
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
DSMP	Data safety monitoring plan
DXA	Dual-energy X-ray absorptiometry
FACS	Fluorescence activated cell sorting
FDA	Food and Drug Administration
FFQ	Food frequency questionnaire
FIT	Fracture Intervention Trial
FLEX	FIT Long-term Extension

FN	Femoral neck
F_u,N	Ultimate force
F_y,N	Yield force
GCP	Good Clinical Practice
HIPAA	Health Insurance Portability and Accountability Act of 1996
HPT	Hyperparathyroidism
HR-pQCT	High resolution peripheral quantitative computed tomography
ICF	Informed consent form
ICH	International Conference on Harmonisation
IGF-1	Insulin-like growth factor 1
IND	Investigational new drug
IRB	Institutional Review Board
ITT	Intention-to-treat
IV	Intravenous
KO	Conditional knockout
LS	Lumbar spine
Micro-CT	Microcomputed tomography
mRNA	Messenger ribonucleic acid
MSE	Margin of sample error
Na	Sodium
NIH	National Institutes of Health
OB	Osteoblast
OC	Osteoclast
OPG	Osteoprotegerin
P1NP	Procollagen Type 1 N-terminal Propeptide
PaTH	PTH and Alendronate for Osteoporosis
PBMC	Peripheral blood mononuclear cells
PBO	Placebo
PD	Pharmacodynamic
PI	Principal Investigator
PICS	PTH and Ibandronate Combination Study
PK	Pharmacokinetic
PTH	Parathyroid hormone
PTH-R	Parathyroid hormone receptor type 1
RAND	Randomization
RANK-L	Receptor activator of nuclear factor kappa B ligand
RCT	Randomized controlled trial
rRNA	Ribosomal ribonucleic acid
SAE	Serious adverse event

SAP	Statistical analysis plan
SC	Subcutaneous
SD	Standard deviation
SFVAHCS	San Francisco VA Health Care System
SFVAMC	San Francisco VA Medical Center
SMI	Structure model index
S,N/mm	Stiffness
Tb	Trabecular
TbBV/TV	Trabecular bone volume/tissue volume
TBS	Trabecular bone score
TPTD	Teriparatide
TSH	Thyroid stimulating hormone
UCSF	University of California, San Francisco
UP	Unanticipated problem
VA	Veterans Affairs

PROTOCOL SYNOPSIS

TITLE	Novel Combination Therapy for Osteoporosis in Men
SPONSOR	Department of Veterans Affairs
FUNDING ORGANIZATION	Department of Veterans Affairs
NUMBER OF SITES	1
RATIONALE	Osteoporosis and fracture-related disability are key health problems in older men. Fractures increase mortality. Men who fracture their hips have twice the mortality of women sustaining those same hip fractures. Several drugs are approved to treat osteoporosis in men [bisphosphonates, denosumab, and teriparatide (TPTD) or PTH(1-34)], but we have little insight as to how to use them most effectively. TPTD has great appeal for treating osteoporosis in men because it substantially improves bone mass, rebuilds the microarchitecture, improves bone strength, and reduces fractures. Little is known about the best ways to employ TPTD in the treatment of male osteoporosis. Should it be used only as monotherapy or does concurrent or sequential use with other agents lead to the greatest benefit? The proposed clinical trial is an effort to test a novel combination therapy for osteoporosis in men based on exciting preclinical findings in mice. It is known that TPTD achieves its anabolic effects by stimulating PTH receptors (PTH-Rs) in cells of the osteoblast (OB) lineage. Calcimimetics mimic the effects of high extracellular calcium concentrations ($[Ca]_e$) by activating Ca-sensing receptors (CaSRs) expressed in many cell types including OBs and osteoclasts in bone. The randomized, double-blind, placebo-controlled trial we will conduct will test the hypothesis that concurrent activation of PTH-Rs and CaSRs (TPTD+calcimimetic cinacalcet) in 48 men with low bone mineral density (BMD) produces greater anabolic responses than PTH-R activation alone (TPTD+placebo).
STUDY DESIGN	Randomized, placebo-controlled, double-blind clinical trial with two treatment arms
PRIMARY OBJECTIVE	Examine the effects on lumbar spine bone mineral density (BMD) by dual energy xray absorptiometry (DXA) of treatment with the combination of TPTD (PTH 1-34) + placebo vs TPTD + oral calcimimetic cinacalcet in men with low bone mass or osteoporosis
SECONDARY OBJECTIVES	- Assess the effects of the combination of TPTD (PTH 1-34) + placebo vs TPTD + oral calcimimetic cinacalcet on femoral neck BMD by DXA in men with low bone mass or osteoporosis - Assess the effects of the combination of TPTD (PTH 1-34) + placebo vs TPTD + oral calcimimetic cinacalcet on the bone formation marker serum N-terminal pro-peptide of type 1 collagen (P1NP) in men with low bone mass or osteoporosis <u>Safety endpoints:</u> - Establish the physiologic responses and parameters related to safety in men treated with these two combination therapy regimens by

	measuring (a) acute and chronic changes in the concentrations of serum calcium ([Ca]) and plasma intact PTH after drug administration (8 hour pharmacodynamic study) and (b) changes in 24 hour urinary Ca excretion (over full 11 month trial) with both treatment regimens.
NUMBER OF SUBJECTS	48 randomized: Teriparatide (TPTD) or PTH(1-34) + placebo tablet: N=24 Teriparatide (TPTD) or PTH(1-34) + cinacalcet tablet: N=24
SUBJECT SELECTION CRITERIA	Study population: We will randomize 48 subjects in our study. Men of all ethnic and racial groups will be encouraged to participate. The DXA scan done at screening will be used to determine whether or not a man meets BMD criteria for enrollment into the study. <u>Inclusion Criteria:</u> • Males aged 50-90 years • DXA BMD T-score ≤ -2.0 at either lumbar spine (LS), femoral neck (FN) or total hip (TH) sites; or DXA BMD T-score ≤ -1.5 with at least one additional important clinical risk factor for osteoporotic fracture [e.g., fragility fracture after age 50 years; parental history of hip fracture; history of hypogonadism, prior glucocorticoid therapy (>3 months prior), current smoking, prevalent vertebral fracture(s), or prior hyperthyroidism on stable treatment] • At least 2 LS vertebral levels with reliable BMD values (i.e., at least 2 without compression or hardware) <u>Exclusion Criteria:</u> • Metabolic bone disease other than osteoporosis (e.g., Paget's disease, HPT or hyperparathyroidism) • Any osteoporosis drug therapy within 12 months; any prior course of TPTD for >3 months • Prior oral bisphosphonate use: if duration of use is <6 months (must have stopped use for ≥ 1 year before randomization); if duration of use is 6-24 months (must have stopped use for >2 years before randomization); if duration of use is >24 months (must have stopped use for > 3 years before randomization) • Prior intravenous bisphosphonate use: if one dose (5 mg) intravenous zoledronic acid was given (must have received it >2 years before randomization); if 2 or more doses (5 mg) intravenous zoledronic acid were given (must have received them >3 years before randomization) • If a different intravenous bisphosphonate was given, if a dose of less than 5 mg of zoledronic acid was given, if intravenous dosing was off-schedule (not every 12 months) for zoledronic acid or another intravenous bisphosphonate, or if there was intermittent compliance (stopping and starting) with oral bisphosphonate therapy, the PI will employ discretion in determining eligibility of the subject for the study. • Use of denosumab (within the past 3 years or >3 injections ever) • Oral glucocorticoid use (≥ 5 mg prednisone) taken within 3 months prior to enrollment • Hypercalcemia (albumin-corrected serum [Ca] >10.2 mg/dL), hypocalcemia (albumin-corrected serum [Ca] <8.8 mg/dL), elevated intact PTH level, or hypercalciuria (urinary Ca >300 mg/24 hours) at screening

	• 25 OH vitamin D levels <20 ng/ml or >80 ng/ml at screening • Estimated glomerular filtration rate <30 ml/min (chronic kidney disease (CKD) stage 4 or 5) • Cancer within past 5 years except for non-melanomatous skin cancers and except for cancers that have been deemed low risk or in remission by appropriate cancer-treating provider and stable for at least 3 years (e.g., noninvasive low grade primary papillary urothelial carcinoma or microcarcinoma of the thyroid such as papillary thyroid) • History of skeletal radiation, prior history of osteosarcoma or bone metastases • Substance abuse (>3 drinks/day), liver disease or impaired liver function (abnormal liver function tests defined as greater than 3 times the upper limit of normal), known cirrhosis, malabsorption • Poorly controlled diabetes (A1c $\geq$9.0%) or current thiazolidinedione therapy • Drugs metabolized through CYP2D6 (e.g., flecainide, tricyclic antidepressants, itraconazole, ketoconazole) • Testosterone therapy with dose change within last 12 months; or androgen deprivation therapy (ADT) within 12 months • Thyrotropin (TSH) level <0.01 • Congenital long QT syndrome, history of QT interval prolongation, family history of long QT syndrome or sudden cardiac death, and other conditions that predispose to QT interval prolongation and ventricular arrhythmia • Hypersensitivity to teriparatide or any excipients in Forteo • Use of other calcium-lowering drugs (e.g., calcitonin, bisphosphonates, denosumab) • Moderate to severe hepatic impairment • High risk for active urolithiasis, defined as having passed a kidney stone clinically within the last 5 years • Upper gastrointestinal bleeding with a history of a clinical episode of upper gastrointestinal bleeding within the last 10 years that was not definitively treated by a surgical procedure • Orthostatic hypotension or a known history of orthostatic hypotension documented in the chart or provided by the patient upon clinical history-taking • Impaired cardiac function either diagnosed symptomatic heart failure or heart failure requiring medical therapy • Average LS T-score by DXA > +1.0 • Underlying spinal disease such as diffuse idiopathic skeletal hyperostosis or Baastrup's disease
TEST PRODUCT, DOSE, ROUTE OF ADMINISTRATION	Teriparatide (TPTD) or parathyroid hormone (PTH) 1-34 which will be obtained by purchase from Eli Lilly Inc; dose 20 mcg daily, by subcutaneous injection Cinacalcet or Sensipar, an oral calcimimetic which will be obtained by purchase from Amgen; dose 30 mg daily, by mouth
CONTROL PRODUCT, DOSE, ROUTE OF ADMINISTRATION	The placebo control will be a tablet purchased from Valor Pharmacy containing inert materials Supplements in the form of calcium citrate tablets (200 mg tablets) will be given in both treatment arms to subjects along with vitamin D3 (1,000

	International Units or a dose to optimize 25 OH D level) by mouth daily. Ca supplements will be adjusted along with an assessment of dietary Ca intake to reach a total of ~1,000 mg elemental Ca per day.
DURATION OF SUBJECT PARTICIPATION AND DURATION OF STUDY	<u>Duration of study participation</u> Subjects will be on study for approximately 12-13 months: Screening: 1-2 visits with flexible timing Run-in period: 4 weeks Intervention period: 11 months <u>Time required for study visits</u> • Screening Telephone Call: to initiate contact, describe the study, and set up a visit to achieve informed consent and to do the screening DXA scan. 30 min • Screening Visit 1 - including trip to DXA lab: 90 min • Screening Visit 2: 90 min • Randomization Visit (with Pharmacodynamic Study): 9 hours or Randomization Visit (without Pharmacodynamic Study): 2 hours • Visit - Week 1 (labs + telephone visit + optional in-person visit): 30 min • Visit - Week 4: 1 hour • Visit – Week 8 (approximately 2 months): 1 hour • Visit – Week 12 (approximately 3 months): 1 hour • Visit – Week 20 (approximately 4 months): 1 hour • Visit – Week 24 (approximately 6 months): 1 hour • Visit – Week 36 (approximately 9 months): 1 hour • Visit – Week 48 (approximately 11 months, including final DXA): 2 hours Total: approximately 21 hours (if the Pharmacodynamic Study is done), approximately 14 hours (if the Pharmacodynamic Study is not done)
OTHER INTERVENTIONS	Participants will be provided calcium supplements at an individualized dose combined with the calcium in their usual diets to achieve a total calcium intake of approximately 1,000 mg/day. This will replace any usual calcium product a subject is taking prior to enrollment. 1,000 units of vitamin D3 daily will also be given to each subject each day.
PRIMARY ENDPOINT	11-month change in lumbar spine (LS) BMD by DXA
SECONDARY ENDPOINTS	• 11-month change in femoral neck (FN) BMD by DXA • 3-month change in the bone turnover marker (BTM) serum N-terminal pro-peptide of type 1 collagen (P1NP)
OTHER MEASUREMENTS	<u>Dietary intakes</u> – Block Food Frequency Questionnaire (baseline only and study end) <u>Pharmacodynamic (PD) testing of three types:</u> (1) assessment of acute changes in the serum levels of calcium, albumin, phosphate and PTH during the acute administration of the study drugs during an 8-hour PD test in the clinic at the Randomization Visit; (2) assessment of chronic changes in the serum levels of calcium and PTH during the entire study with the administration of the study drug combinations; (3) assessment of chronic changes in the urinary calcium during the entire study at study visits as outlined in the Protocol. <u>Other hormonal and metabolite/BTM testing:</u> serum levels of 1,25(OH)₂ vitamin D, the following BTMs (C-telopeptide, bone specific alkaline

	phosphatase, osteocalcin) and the bone regulating molecules osteoprotegerin (OPG) and the receptor activator of nuclear factor kappa B ligand (RANK-L) <u>Additional laboratory testing</u> – peripheral blood mononuclear cells will be collected and analyzed by FACS analysis for circulating osteoblast and osteoclast precursors to gain insight into the cellular mechanisms that may be responsible for the changes in bone mass and metabolism observed in the study. <u>Use of DXA to determine trabecular bone score (TBS):</u> – this measurement will be done on the data collected from the routine spine DXA done at baseline and after 11 months of treatment
SAFETY EVALUATIONS	At each study visit, subjects will be queried in an open-ended manner about any adverse events that occurred since the last phone call or in-person visit. 24 hour urine collections will be done throughout the study looking for any changes in urinary calcium excretion.
PLANNED INTERIM ANALYSES	Comprehensive progress reviews of safety and efficacy data will be performed at least annually by the VA CSR&D Data Monitoring Committee. Unless requested by the DMC, interim analyses of between-group differences in the efficacy outcomes are not planned, as this is a trial of modest size and duration with an active comparator group. Early stopping of the trial for benefit, harm, or futility with respect to the primary endpoint is highly unlikely to be necessary. The Medical Monitor will meet with the PI and other members of the study team at the beginning of the trial and then every 2 to 4 weeks to review any adverse events (AEs) and any protocol deviations that might occur. The Medical Monitor will also review serum calcium values that are returning to the trial in real-time. The Medical Monitor will not have any direct involvement in the conduct of the trial.
STATISTICS General Considerations	General statistical considerations: Statistics will include descriptive as well as analytic approaches. We will use an intention-to-treat (ITT) approach, with all randomized men included in the analysis. We will attempt to collect complete follow-up data on every randomized subject, regardless of adherence. 2° per-protocol analyses will be done, limited to those who remained on medication and those with complete data. All statistical testing will be performed at nominal 0.05 level without adjustments for multiple comparisons.
Primary Analysis Plan	<u>AIM 1: To determine the effects of 11 months of treatment with TPTD+cinacalcet compared to TPTD+PBO on BMD and bone metabolism in men with low bone mass. We will assess responses in: (a) LS BMD (primary endpoint) and FN BMD; and (b) levels of the bone formation marker P1NP.</u> Testing the 1° hypothesis for the effect of the 2 treatment arms on the % change in LS BMD will use a t-test with a two-sided significance level of 0.05 (1). A similar approach will be taken for FN BMD and for the logarithm of the P1NP change, both 2° endpoints. On an exploratory basis, changes in TBS from baseline to study end will be analyzed as BMD is. <u>AIM 2: To determine pharmacodynamic (PD) responses to TPTD+cinacalcet and to TPTD+PBO treatment in men with low bone</u>

	<u>mass. To establish physiologic response and confirm parameters of combination therapy, we will assess: (a) acute and chronic changes in the serum [Ca] and plasma intact PTH after drug administration; and (b) changes in urinary Ca excretion with both treatment regimens.</u> Serum and urinary Ca are key safety parameters. Effects will be assessed in several ways. For the 24 men who have the 8-hour PD testing with drug administration at the Randomization Visit, we will plot mean and standard deviation (SD) of acute change in serum [Ca] from pre-dose to post-dose over 2, 4 and 8 hours. However, our main safety endpoint will be the proportion in each treatment group who decrease to >5% below the lower limit of normal at 8 hours after dosing. We will compare the proportions between groups using a chi square test. We will also compare the 2-, 4-, and 8-hour changes between groups using a t-test. We will also examine, in all 48 men, the mean serum [Ca] and PTH chronic changes from baseline to 1, 2, 3, 6, 9, and 11 months of treatment and test the null hypothesis (using a t-test) that there is no difference between treatment groups at for any time period. Urinary Ca will be measured (pre-dose) at baseline and at 1, 3, 6, 9, and 11 months. We will compare the proportions of subjects in each treatment group with 24-hour urinary Ca >350 mg.
Rationale for Number of Subjects	AIM 1: A sample size of 48 men (24/group) will provide 80% power with alpha=0.05 to detect a difference as small as 3.7% between the LS BMD responses of men treated with TPTD+cinacalcet vs TPTD+PBO. Even if 20% of our subjects were lost to follow-up and did not contribute 11-month LS BMD data, with a sample size of 40 we would be powered to detect a between-group difference as small as 4.0%. We will have 80% power (with an alpha=0.05) to detect a between-group difference in change in FN BMD as small as 3.5%. A sample size of 40 (20/group, assuming 20% non-completers) will provide 80% power with alpha=0.05 to detect a difference of +137% (e.g., an increase from 148% to 285%) between P1NP responses of men treated with TPTD+cinacalcet vs TPTD+PBO. AIM 2: A sample size of 40 (20/group, assuming 20% non-completers) will provide 80% power with alpha=0.05 to detect a between-group difference of approximately 0.43 in the proportion of subjects who cross the threshold of serum Ca >5% below the lower limit of normal or of 24-hour urine Ca >350 mg. Literature References: 1. Moser BK, Stevens GR, Wallis CL. The two sample t-test versus Satterthwaite's approximate F-test. Comm Stat Theory Math 18: 3963-75, 1989. 2. Orwoll ES, Scheele WH, Paul S et al: The effect of teriparatide [human parathyroid hormone (1-34)] therapy on bone density in men with osteoporosis. J Bone Miner Res 18:9-17, 2003. 3. Black DM, Greenspan SL, Ensrud KE et al: The effects of parathyroid hormone and alendronate alone or in combination in postmenopausal osteoporosis. N Engl J Med 349:1207-15, 2003.

1 BACKGROUND

1.1 Overview of Clinical Studies

1.1.1 SIGNIFICANCE:

What Is the Risk of Osteoporotic Fractures in Men and Why Do Men Lose Bone Mass?

Osteoporosis is a neglected condition in men. Yet, men sustain approximately 30% of the 1.5 million fractures that occur annually in the US. Fractures are expensive. Estimated costs are at least \$20 billion annually. This figure will no doubt rise substantially as the population ages. Plus, these costs do not take into account the personal and societal burden of fractures, especially hip fractures. One in 6 men will sustain a hip fracture by the time he reaches age 90 years (1). A man who fractures a hip at any age has greater disability following that fracture and is much less likely to regain his ability to walk and to live independently afterward. Men also have a greater risk of dying from the complications of hip fractures. Overall, one-year mortality for patients who sustain a hip fracture is ~20%. However, mortality in men with hip fractures is staggeringly high at ~37.5% in the first year (1).

The pathophysiology of bone loss in aging men differs in important ways from postmenopausal osteoporosis. Age-related bone loss in men begins in the 6th decade with nutritional and hormonal abnormalities playing important roles. Contributing factors include decreased intestinal Ca absorption, vitamin D deficiency or insufficiency, and secondary (2°) HPT. Testosterone levels decline with age in men, and as they do, estradiol levels also fall. Considerable evidence supports an important role for estradiol in maintaining bone mass in men as well as women (2,3). Men lose both trabecular and cortical bone mass with age. Trabecular bone thins out in men, rather than perforates, as it does in women, and excessive cortical bone remodeling is a dominant force in older men. In men, periosteal bone apposition does not keep pace with endosteal resorption, and the bones weaken. With minimal trauma, fragility fractures may result. Thus, reduced bone formation is a key mechanism underlying bone loss in men, more so than the high rates of bone resorption seen in postmenopausal estrogen deficiency. For these reasons, anabolic regimens that enhance bone formation may achieve better clinical outcomes in men compared to commonly used antiresorptive agents. This trial will test a novel anabolic combination therapy in men.

How Effective Are Current Treatments for Osteoporosis in Men?

Several agents have been Food and Drug Administration (FDA)-approved to treat osteoporosis in men: bisphosphonates; denosumab; and teriparatide (TPTD) or PTH (1-34). In trials enrolling men, these agents were shown to increase BMD by dual energy X-ray absorptiometry (DXA) at key skeletal sites, quantitatively similar to their effects in postmenopausal women (4,5). In only a few appropriately powered studies, there was a reduction in incident vertebral fractures in men at high risk and/or those on androgen deprivation therapy.

Intermittent injections of TPTD are appealing as a treatment for osteoporosis in men because the agent has potent anabolic actions. TPTD increases bone formation, reflected by enhanced biochemical markers of osteoblast (OB) activity, such as N-terminal propeptide of type 1 collagen (P1NP) and bone specific alkaline phosphatase (BSAP) in the blood, and by direct histomorphometric quantification of bone formation, and mineral apposition rates. TPTD also improves the microarchitecture of bone by micro-CT (trabecular thickness and connectivity) and increases the maturation or number of circulating osteogenic precursors and stem cells in blood in postmenopausal women. TPTD in vitro stimulates the proliferation of mesenchymal stem cells and their commitment to the OB lineage as osteoprogenitors. PTH (1-34) also increases differentiation of early OBs and matrix production, blocks apoptosis of OBs and osteocytes, and reduces production of the Wnt inhibitor sclerostin by osteocytes. The anabolic actions of PTH treatment within a defined time-frame (18 to 24 months in humans) -- called the

“anabolic window” -- improve bone strength and ultimately reduce spine and nonvertebral fractures. Over time, however, PTH stimulates RANK-L production by early OB lineage cells, and RANK-L enhances osteoclast (OC) production. This increases bone resorption, which limits further gains in BMD with PTH. The challenge in designing optimal treatment regimens with PTH is maximizing its anabolic activity, while taming its catabolic effects on bone.

Clinical trials with TPTD [recombinant human PTH (1-34)] or synthetic human PTH (1-34) in men are limited to a few studies with small numbers of men. Orwoll et al (6) randomized 437 men into 3 groups: placebo (PBO) vs 20 (the dose subsequently FDA-approved) or 40 ug TPTD daily. However, they completed only an average of 11 months on treatment. Kurland et al (7) randomized 23 men to synthetic PTH (1-34) (400 IU or ~25 ug/day; N=10) or PBO (N=13) for 18 months. Finkelstein et al (8), as part of a combination study, randomized 27 men to synthetic PTH (1-34) for 24 months (37 ug/day). Thus, that study used twice the approved dose of PTH (1-34). Walker et al (9) randomized men to risedronate (35 mg/week) (N=10), TPTD (20 ug/day) (N=9), or the combination (N=10) for 18 months. In these 3 studies, BMD rose by ~6-14% at the LS and by ~2-4% at FN sites with 11-18 months treatment [with 20 or 25 ug PTH (1-34)/day] (6-9). Higher doses of PTH (1-34) (37 or 40 ug/day) (12,14) produced even greater responses at both sites (2-3 fold more). This indicates that stronger anabolic effects are feasible to achieve in men within these short time-frames. However, these doses are less tolerated, and we do not plan to use them. Rather, we will use the FDA-approved dose of TPTD (20 ug/d).

Combination studies of PTH (1-34) with alendronate (8) or TPTD with risedronate (9) did not convincingly show synergistic effects on BMD in men. A trial combining TPTD and denosumab showed additive effects of the combination, but it was done in women (10). Several important questions about TPTD treatment in men have never been addressed. Among them, can TPTD be advantageously combined with another “bone-active” drug that has a similar or a different mechanism of action? We only know that adding PTH (1-34) to alendronate in men does not produce additive effects. This trial will test the hypothesis that concurrent CaSR activation (by calcimimetic) synergizes with PTH-R activation (by TPTD) to produce greater anabolic effects in men, reflected by changes in BMD and bone turnover markers (BTMs), compared to TPTD alone. This is a novel combination therapy that is well-supported in preclinical studies (11).

1.1.2 SCIENTIFIC PREMISE FOR AN INTERVENTION

Introduction: This is a first in human study for the combination therapy that will be tested in this trial. Both of the drugs that will be used in the trial have been FDA-approved for many years and have been used in the clinic in hundreds of thousands of patients worldwide: teriparatide (TPTD) for the treatment of osteoporosis in women and men, and cinacalcet for the treatment of hyperparathyroidism in women and men. The two agents to be used in the trial have not been as yet tested in the combination format that will be done in this study. Summarized below are preclinical data from young (12 week old) and elderly (12 month old) male and female mice.

Preclinical Studies: Combined PTH(1-34) and Calcimimetic Produce Marked Anabolic Effects on Bone in Mice

Efficacy. Our laboratory has worked on the local control of bone remodeling by extracellular [Ca]/CaSRs and by PTH/PTH-Rs. In conditional (or tissue-specific) knockout mice, we showed that the CaSR played a key role in skeletal development and in osteoblast (OB) and osteocyte function (12). This work suggested that high extracellular [Ca] ([Ca]_e), acting through the CaSRs, is an “anabolic pathway” in bone, akin to intermission PTH (1-34) and PTH-R signaling. Furthermore, we and others also found that direct CaSR activation in OC lineage cells reduced their survival, gene expression, and resorptive function (11). This suggested that enhanced OB and suppressed OC function might be accomplished through activation of CaSRs in different bone cell populations.

Based on this work in mice and the known role of PTH peptides as bone anabolics in humans, we tested the hypothesis that concurrent activation of PTH-Rs and CaSRs has synergistic effects on bone mass in mice (13). Adult male mice given intermittent subcutaneous (SC) injections of PTH(1-34) (40-80 ug/kg) and the calcimimetic NPS-R568 (20 umole/kg) for 4-6 weeks showed dramatic synergistic anabolic effects on bone mass and strength. PTH (1-34) injections alone significantly increased trabecular (Tb) bone mass [Tb bone volume/tissue volume (BV/TV)] by micro-CT in the distal femur as well as Tb thickness (TbTh) ($p < 0.05$). Co-injections of PTH (1-34) and NPS-R568 produced significantly greater effects on Tb BV/TV and TbTh (by ~21%; $p < 0.01$), while NPS-R568 injections alone had no effect. These are large effects on bone mass, as determined by highly sensitive methods—micro CT and histomorphometry. We also showed that the combination therapy produced bone microarchitectural changes (more plate-like trabeculi), compatible with mechanically stronger bone.

Cortical (Ct) bone is typically less affected by PTH (1-34) treatment. However, when we assessed Ct bone at the tibiofibular junction (TFJ) by micro-CT, we found that combined injections of PTH (1-34) and NPS-R568 produced dramatic increases in CtTV, CtBV, and CtTh of 8-10% ($p < 0.05$). Thus, this work demonstrated clear “anabolic synergy” of concomitant PTH-R and CaSR activation on both Tb and Ct bone in adult male mice – findings potentially clinically significant and relevant to the proposed trial. Similar and dose-dependent increases were seen in Tb bone of the L5 vertebrae [in BV/TV, TbTh, and Tb number (N); $p < 0.05$ or $p < 0.01$] and in their Ct bone at the TFJ (CtTV, CtBV, and CtTh; $p < 0.05$) in elderly female mice.

We did dynamic histomorphometry on bone biopsy specimens in the mice. Histomorphometry of bone is a “gold standard” test for the activity of a treatment active on bone. Daily injections for 6 weeks of TPTD alone induced substantial bone formation by fluorescent tetracycline labelling from Ct bone sections. Bone formation was substantially augmented by co-administration of calcimimetic NPS R568. Quantitative analyses of Tb and Ct bone parameters (N=12 mice/group) support the micro-CT data noted above, indicating robust strong increases in bone mass with this combination. My mechanical testing of the mouse femurs, we showed that bone was stronger (greater energy to failure) in male mice treated with combined PTH/NPS-R568 vs PTH (1-34)+vehicle.

Safety. We assessed effects of these treatments on serum [Ca] in male mice at specific time-points after drug injection. 3 hours post-injection, serum [Ca] (mg/dL) was 8.64 ± 0.08 [vehicle]; $9.40 \pm 0.13^{**}$ [PTH (40 mcg/kg)]; $8.65 \pm 0.08^{*}$ [PTH (40 mcg/kg) + NPS R568 (20 umol/kg)]. 24 hours post-injection, serum [Ca] (mg/dL) was 9.37 ± 0.14 [vehicle]; $10.0 \pm 0.25^{**}$ [PTH (40 mcg/kg)]; and 9.26 ± 0.20 [PTH (40 mcg/kg) + NPS R568 (20 umol/kg)] (N=15-24 mice); $*p < 0.05$, $**p < 0.01$ vs vehicle). Mice treated with PTH (1-34) alone showed mild increases in serum [Ca], but these effects were *abrogated* by co-administration of NPS-R568.

1.1.3 IMPACT

This clinical trial is highly relevant and important to the health of male veterans. Osteoporosis in men is a neglected topic. There are many risk factors for low bone mass and increased fracture risk in men: advanced age, smoking, chronic obstructive pulmonary disease, glucocorticoid therapy, diabetes, ADT for prostate cancer, alcohol abuse, malabsorption, liver disease, testosterone deficiency, and others. So many of these predisposing factors are strongly represented in male veterans and contribute to their heightened fracture risk. Fully 50-70% of men have 2° causes for osteoporosis. Plus, there is also a subgroup of men who present in middle age (<70 years), often with vertebral fractures and/or low BMD whose disease goes unexplained, earning the diagnosis of idiopathic 1° male osteoporosis. They have many years of life expectancy and remain at risk for fracture. This trial will enroll male veterans and test a

novel combination anabolic regimen of 2 approved drugs under controlled conditions. Our findings will be key in designing evidence-based regimens for men with low bone mass and at high fracture risk.

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2 STUDY RATIONALE

The objective of the proposed clinical trial is to compare treatment with TPTD alone to a novel combination of TPTD and cinacalcet in men with low bone mass. Activating PTH/PTH-related protein receptors (PTH-Rs) with TPTD directly stimulates bone formation by enhancing the recruitment of mesenchymal stem cells and differentiation of osteoblast (OB) lineage cells. The calcimimetic cinacalcet activates extracellular calcium-sensing receptors (CaSRs) in parathyroid and many other cells and is approved to treat hyperparathyroidism (HPT). Our studies in mice indicate that expression and activation of CaSRs in early and/or late OBs promote their differentiation, survival, and mineralizing capacity. We found that combined PTH (1-34) and the investigational calcimimetic NPS-R568 produced dramatically greater skeletal anabolic responses than PTH (1-34) alone in mice. This trial will test the novel combination of

TPTD+cinacalcet vs TPTD+placebo (PBO) in men with low BMD and assess responses in bone mass and turnover and in biochemical, hormonal, and safety parameters.

2.1 Risk / Benefit Assessment

The risks involved in this clinical trial are reasonable in relation to the possible benefits that a subject may accrue and that may result to society. Specifically:

With respect to the subject: The subject will receive a thorough assessment of his skeletal status and his overall general health through medical history taking and physical examination, DXA scan review, comprehensive lab testing and visits with the study team. These services will complement what he is receiving from his primary care provider as he will get special attention to skeletal status and risk factors for further bone loss. He will have a dietary Ca history taken and intake quantified. This is outside the realm of daily practice, but is valuable in that nutritional recommendations are part of the foundation for the maintenance of good bone health with aging. He will get enhanced monitoring of Ca excretion and renal function over the course of the full study. This is not typically part of routine care. In addition, he will be randomized to receive either teriparatide (plus placebo) -or- teriparatide (plus cinacalcet) – the two study arms. He will, therefore, receive a highly effective medication (teriparatide) for low bone mass or osteoporosis, regardless of what arm of the study he is randomized to. He will further receive Ca and vitamin D3 supplements tailored to his needs as part of both study arms. He will, therefore, receive enhanced monitoring and care, an active medication, nutritional supplements, and education about male osteoporosis in the course of being cared for by the study team. Finally, he will be making a contribution to under-studied areas of men's health - male osteoporosis and effective therapies for men at risk for fractures.

With Respect to Society: Male osteoporosis is an under-studied area of medicine and of men's health. Yet, men suffer the consequences of declining BMD and fractures and have a higher rate of morbidity and mortality after fractures, like those of the hip, than do women. 1/3 of all osteoporotic fractures occur in men. ~37% of men who have a hip fracture die in Year 1 after that fracture. This study will contribute to the limited knowledge we have of male osteoporosis, using an innovative combination therapy for the condition, which targets two sets of receptors on osteoblasts (the PTH receptor and the Ca sensing receptor). Therefore, this study has the potential to contribute new knowledge and to support this particular combination therapy. If this combination is effective, even mildly so, in stimulating synergistic increases in BMD, then research on it can be expanded (and the regimen optimized) to target other forms of osteoporosis - postmenopausal, glucocorticoid-induced and so forth. We are using two already FDA-approved medications, thus if successful, the drugs we will be using are already on the market. Thus, a positive result here tests an important hypothesis which could impact treatment of osteoporosis of other etiologies (with a greater dividend to Society).

2.1.1 RESEARCH-RELATED RISKS

1. Risks associated with radiation exposure for imaging studies specifically for research purposes
2. Risk of pain or physical discomfort caused by the research intervention
3. Possible personal discomfort due to sensitive topics (stress, embarrassment, trauma)

2.1.2 POSSIBLE RISKS

Interventional studies, risk that the regimen may be more harmful or less effective than other available interventions:

We intend to do careful monitoring of our participants to avoid harm. The two potential very specific side-effects or harms we might see would be: lowering of the serum calcium level due to cinacalcet, which could cause immediate side-effects; or an increase in the serum calcium level due to unopposed teriparatide, which could cause side-effects. If either were to occur, the effect expected would be mild. Low blood calcium levels could cause difficulty concentrating, poor memory, fatigue, muscle cramps, numbness around the mouth and in the fingertips, according to the level of severity, and this abnormality in blood tests may cause no symptoms at all, if it is mild. We will be using a small dose of cinacalcet (30 mg, the smallest marketed dose of the drug in the US) in the trial, and we expect any serum calcium lowering effect to be quite mild. Nevertheless, participants will be told about this. A mild elevation in the serum calcium level, if persistent and not just transient due to the immediate action of PTH(1-34) or teriparatide, could cause thirst, headache, fatigue, excessive urination, constipation, or no symptoms at all.

Both teriparatide and cinacalcet can have less specific side-effects such as nausea, vomiting, leg cramps, headaches, joint pains, muscle pains and other complaints as detailed in their Prescribing Information. These are standard adverse events that will be closely monitored for in this trial setting. There may be a rare risk of gastrointestinal bleeding due to cinacalcet. This will be asked about during our clinical study encounters. The cause is unknown but may occur in those at greater risk for such complications with underlying gastritis and esophagitis. Subjects with a history of unexplained gastrointestinal bleeding will not be included in the study. Changes in serum calcium levels will be looked at both chronically and acutely in this study by lab tests and will come under the watch of our Medical Monitor, an experienced endocrinologist (Dr. Tiffany Kim) who is not involved in the conduct of the study.

Changes in urinary calcium levels will be looked at throughout the study with the 24-hour urine calcium monitoring that will take place. Concern would be for a marked increase in urinary calcium levels which would be picked up by the lab testing.

Teriparatide is one of the two or three most effective interventions that are available for treatment of severe osteoporosis in clinical use. These 3 interventions (teriparatide, abaloparatide, and denosumab) are about equipotent in terms of fracture risk reduction. So we feel confident we are not giving our subjects a "less effective" intervention for their underlying condition.

Our informed consent document contains a reference to the occurrence of osteosarcoma in rats treated with high doses of teriparatide for long periods of time (e.g., the number of years equivalent to the lifespan of the rat). This is a theoretical concern since this complication has not been seen in humans exposed to teriparatide for nearly 20 years of clinical use. However, this theoretical concern led the Food and Drug Administration (FDA) to place a "black box warning" on teriparatide, and for that reason, this was mentioned in the original consent document. The "black box warning" was removed from the package insert for teriparatide or Forteo in 11/2020 by the FDA, and we will remove this information from our study consent form as this is no longer relevant or represents the view of the FDA on this medication.

Risks associated with radiation exposure for imaging studies specifically for research purposes:
The radiation dose due to a DXA Scan, which will be done at screening to determine eligibility for and as a baseline for the study and at the end of the study, is very small and is considered low-dose radiation. DXA delivers about 0.001 mSv per study. Please note: the average person in the U.S. receives an effective dose of about 3 MSv per year from natural radiation and cosmic

radiation from outer space. These natural "background doses" vary according to where you live. A coast-to-coast round-trip airline flight delivers about 0.03 mSv due to exposure to cosmic rays. The largest source of background radiation comes from radon gas in our homes (about 2 mSv per year).

Risks of pain or physical discomfort caused by the research intervention: We will minimize the risk of pain due to venipuncture or the placement of an intravenous catheter to do multiple blood draws for the pharmacodynamic study by having very skilled individuals (nurses, phlebotomists, the PI) doing the procedures. Daily subcutaneous injections of teriparatide could cause pain at the injection site. This is mitigated by the tiny and very short needle that is used on the injection pen. In general, in the PI's experience pain is not a complaint that is offered by patients taking teriparatide. Our subjects will be taught good injection technique and how to deliver the tiny injection volume as painlessly as possible.

Personal discomfort due to sensitive topics (stress, embarrassment, trauma): We will be querying subjects for information about their history of alcohol intake, as it can affect bone mass, and whether or not it is current, which would be highly relevant to the study. This may cause the stress of embarrassment. We will mitigate this by asking these questions in a non-judgmental way and avoid giving any opinion on a sensitive topic.

Hypocalcemia and hypercalcemia: Side effects related these changes in blood tests are listed and described above. Both could theoretically occur due to the types of medications used in the study.

Gastrointestinal symptoms: Calcium supplements can sometimes cause gas, constipation, and reflux. Cinacalcet can cause nausea and less frequently vomiting. These are usually mild gastrointestinal symptoms and do not progress or become disabling.

Kidney stones: Very rarely, if an individual is over-supplemented with calcium, a kidney stone could result. Very rarely, if teriparatide raises the urinary calcium levels to high levels, a kidney stone could result. This was thought to be an insignificant clinical issue by the FDA when teriparatide was being reviewed for approval in ~2001 and it was not required or recommended that 24-hour urine calcium levels be periodically monitored in patients receiving teriparatide for the treatment of osteoporosis.

Nonspecific and systemic symptoms: Malaise, fatigue, muscle cramps could be caused by either agent.

Phlebotomy and IV catheter placement: Phlebotomy and IV catheter placement may cause local pain and bruising and occasionally may result in a hematoma, which can be painful but carries no significant long-term risks. Infections from IV lines rarely occur from such brief placements. However, any signs of inflammation will result in removal of the line and treatment with local heat and hand and arm elevation.

Inconvenience: some individuals may find doing the 24-hour urine collections inconvenient.

Incidental findings: It is possible that tests done as part of this study (for example, lab tests) will reveal abnormalities requiring additional medical evaluation. Should this happen, results will be discussed with the individual, with possible referral to his doctor or health care provider for additional follow-up and evaluation.

Confidentiality: Participation in research may lead to unintentional loss of privacy. Although the data will be coded, stored specimens will be de-identified, and publications will not identify participants in any way, there is nevertheless a remote possibility of loss of confidentiality with respect to stored data.

2.1.3 MINIMIZING RISKS

Gastrointestinal symptoms: In the unlikely event that symptoms occur due to either calcium supplements or cinacalcet or placebo and cause meaningful gastrointestinal discomfort, we have a few options to consider. We can lower the dose of calcium supplements. Everyone in the trial will be getting calcium supplements. We can hold them for a few days to see if they are the source of gastrointestinal problems. If there are symptoms of more than transient nausea after the ingestion of cinacalcet or placebo, we will advise the participant to take the study medication (cinacalcet or placebo) with food. If the problem persists, is severe, or very troublesome to the subject, he can discontinue study drugs and be referred to his clinician for ongoing monitoring and followup.

Changes in serum calcium levels: Changes in either direction (increase or decrease in serum calcium levels) will be monitored for chronically with blood tests at each study visit. Acutely serum calcium will be monitored over the first 8 hours after dosing with teriparatide + placebo and with teriparatide + cinacalcet during pharmacodynamic testing. The possible symptoms noted above will be explained to subjects so that they are in a position to assess how they are feeling and what to look for more chronically during the execution of the study as an outpatient. The study's Medical Monitor will be reviewing the serum calcium values in real-time also.

Changes (increases) in urine calcium levels: Changes in urine calcium levels will be monitored chronically over the entire study. If urinary calcium levels rise to over 400 mg per day, we will lower calcium supplements (50%) and reassess urinary calcium levels (2 weeks later) to assure that they have returned to an acceptable level for the subject to stay on the study medications. If urinary calcium levels do not return to a safe level, we will discontinue calcium supplements and reassess urine calcium levels (2 weeks later). If the urine calcium levels do not return to a safe level, then study medications will be discontinued and the patient will be referred to his medical provider for ongoing followup and monitoring.

Kidney stone: In the unlikely event that a kidney stone occurs during the study, the subject will be referred to his provider for treatment as indicated. The subject will have the option to discontinue study medications.

Phlebotomy and IV catheter placement: All blood draws and insertion of IVs will be performed by qualified nurses, phlebotomists or the PI as needed. Any signs of inflammation while an IV is in place will result in removal of the line, treatment with local heat packs and elevation and close monitoring of the site and the subject.

Ionizing radiation: Subjects will be informed about the ionizing radiation exposure levels which are described above, so the subject may make an informed choice about participating.

Incidental findings: Should there be incidental findings that a study physician (the PI or another physician in the study team) feels warrant additional evaluation or intervention, the findings will be discussed with the subject. The subject may be referred to his clinician, and with the participant's permission, the study physician may discuss the findings with the participant's clinician.

Confidentiality: All data will be kept secure and confidential in locked cabinets in locked rooms on locked floors and in password protected electronic files. The data will be coded, stored specimens will be deidentified, and publications will not identify participants in any way.

There will be continuous safety surveillance with emphasis on the potential adverse effects of the intervention and each study procedure. We will respond to any concerns or questions. Participants in the study will be discontinued if the investigators determine that further participation would be detrimental to the participant's health or well-being, and participants may withdraw at any time.

3 STUDY OBJECTIVES

3.1 Primary Objective

Examine the effects on lumbar spine bone mineral density (BMD) by dual energy xray absorptiometry (DXA) of treatment with the combination of TPTD (PTH 1-34) + placebo vs TPTD + oral calcimimetic cinacalcet in men with low bone mass or osteoporosis

3.2 Secondary Objectives

- Assess the effects of the combination of TPTD (PTH 1-34) + placebo vs TPTD + oral calcimimetic cinacalcet on femoral neck BMD by DXA in men with low bone mass or osteoporosis
- Assess the effects of the combination of TPTD (PTH 1-34) + placebo vs TPTD + oral calcimimetic cinacalcet on the bone formation marker serum N-terminal pro-peptide of type 1 collagen (P1NP) in men with low bone mass or osteoporosis

Safety endpoints:

- Establish the physiologic responses and parameters related to safety in men treated with these two combination therapy regimens by measuring (a) acute and chronic changes in the concentrations of serum calcium ([Ca]) and plasma intact PTH after drug administration (8-hour pharmacodynamic study) and (b) changes in 24-hour urinary Ca excretion (over full 11 month trial) with both treatment regimens.

4 STUDY DESIGN

4.1 Study Overview

The study design is that of a randomized double-blind, placebo (PBO)-controlled trial of the combination of teriparatide (TPTD) + the calcimimetic cinacalcet compared to monotherapy with TPTD alone in men with low bone mineral density (BMD).

To address the hypothesis that concurrent calcium-sensing receptor (CaSR) and parathyroid hormone receptor (PTH-R) activation produces synergistic anabolic effects on bone, we will perform a double-blind, PBO-controlled trial in men with low BMD testing a novel combination treatment regimen. Older men with low BMD by DXA will be randomized to 2 treatment arms: TPTD+cinacalcet vs TPTD+PBO. Efficacy endpoints will be changes in BMD by DXA and the bone turnover marker (BTM) amino-terminal propeptide of type 1 collagen (P1NP) (Aim 1). Pharmacodynamic (PD) effects of the combination regimen vs monotherapy will be profiled (serum Ca, PTH) and safety confirmed (Aim 2). A subset of 24 patients (12/treatment arm) will undergo detailed acute (8 hr) PD assessments and clinical monitoring at the UCSF CRC (Clinical Research Center) of which the SFVAHCS (San Francisco VA Health Care System) is part. Safety will be assessed in all trial subjects with serum Ca and 24-hour urinary Ca

monitoring and with adverse event (AE) and clinical assessments over the entire trial. Although both drugs used in this trial are FDA-approved [TPTD, 20 ug/day for osteoporosis; cinacalcet, 30 mg/day for hyperparathyroidism (HPT)], an IND (Investigational New Drug) application will be filed to give this drug combination to men with low BMD or osteoporosis.

4.2 Specific Aims

Aim 1: To determine the effects of 11 months of treatment with TPTD+cinacalcet compared to TPTD+PBO on BMD and bone metabolism in men with low bone mass. We will assess responses in: (a) lumbar spine (LS) BMD (primary endpoint) and femoral neck (FN) BMD; and (b) levels of the bone formation marker serum N-terminal pro-peptide of type 1 collagen (P1NP).

Hypothesis 1a: LS and FN BMD responses are greater with TPTD+cinacalcet compared to TPTD+PBO.

Hypothesis 1b: Serum P1NP increases are greater with TPTD+cinacalcet compared to TPTD+PBO.

Aim 2: To determine the pharmacodynamic responses to TPTD+cinacalcet and to TPTD+PBO treatment in men with low bone mass. To establish physiologic responses and confirm parameters of this combination therapy, we will assess: (a) acute and chronic changes in the concentrations of serum calcium ([Ca]) and plasma intact PTH after drug administration; and (b) changes in 24 hour urinary Ca excretion with both treatment regimens.

Hypothesis 2a: Serum [Ca] does not decrease to > 5% below the lower limits of the normal range in response to the administration of study drugs.

Hypothesis 2b: Urinary Ca excretion does not exceed 350 mg per 24 hours in men treated chronically with study drugs.

5 CRITERIA FOR EVALUATION

5.1 Primary Efficacy Endpoint

11-month change in lumbar spine (LS) BMD by DXA

5.2 Secondary Efficacy Endpoints

- 11-month change in femoral neck (FN) BMD by DXA
- 3-month change in the bone turnover marker (BTM) serum N-terminal pro-peptide of type 1 collagen (P1NP)

5.3 Safety Evaluations

At each study visit, subjects will be queried in an open-ended manner about any adverse events that occurred since the last phone call or in-person visit. (See “Adverse Event Assessment and Recording”, below.)

Serum calcium and 24-hour urine collections will be done throughout the study looking for any changes in urinary calcium excretion. (See “Study Procedures and Guidelines” and “Evaluations by Visit”, below.)

5.4 Other Evaluations

Dietary intakes – Block Food Frequency Questionnaire (baseline and study end)

Pharmacodynamic (PD) testing of three types: (1) assessment of acute changes in the serum levels of calcium, albumin, phosphate and PTH during the acute administration of the study drugs during an 8-hour PD test in the clinic at the Randomization Visit; (2) assessment of chronic changes in the serum levels of calcium and PTH during the entire study with the administration of the study drug combinations; (3) assessment of chronic changes in the urinary calcium during the entire study at study visits as outlined in the Protocol.

Other hormonal and metabolite/BTM testing: serum levels of 1,25(OH)₂ vitamin D, the following BTMs (C-telopeptide, bone specific alkaline phosphatase, osteocalcin) and the bone regulating molecules osteoprotegerin (OPG) and the receptor activator of nuclear factor kappa B ligand (RANK-L) and sclerostin.

Additional laboratory testing – peripheral blood mononuclear cells will be collected and analyzed by FACS analysis for circulating osteoblast and osteoclast precursors to gain insight into the cellular mechanisms that may be responsible for the changes in bone mass and metabolism observed in the study.

Use of DXA to determine trabecular bone score (TBS): – this measurement will be done on the data collected from the routine spine DXA done at baseline and after 11 months of treatment

6 SUBJECT SELECTION

6.1 Study Population

We will randomize 48 subjects in our study. Men of all ethnic and racial groups will be encouraged to participate. The DXA scan done at screening will be used to determine whether or not a man meets BMD criteria for enrollment into the study.

6.2 Inclusion Criteria

- Males aged 50-90 years
- DXA BMD T-score ≤ -2.0 at either lumbar spine (LS), femoral neck (FN) or total hip (TH) sites; or DXA BMD T-score ≤ -1.5 with at least one additional important clinical risk factor for osteoporotic fracture [e.g., fragility fracture after age 50 years; parental history of hip fracture; history of hypogonadism, prior glucocorticoid therapy (>3 months prior), current smoking, prevalent vertebral fracture(s), or prior hyperthyroidism on stable treatment]
- At least 2 LS vertebral levels with reliable BMD values (i.e., at least 2 without compression or hardware)

6.3 Exclusion Criteria

- Metabolic bone disease other than osteoporosis (e.g., Paget's disease, hyperparathyroidism)
- Any osteoporosis drug therapy within 12 months; any prior course of TPTD for ≥ 3 months
- Prior oral bisphosphonate use: if duration of use is < 6 months (must have stopped use for ≥ 1 year before randomization); if duration of use is 6-24 months (must have stopped use for >2 years before randomization); if duration of use is >24 months (must have stopped use for > 3 years before randomization)
- Prior intravenous bisphosphonate use: if one dose (5 mg) intravenous zoledronic acid was given (must have received it >2 years before randomization); if 2 or more doses (5 mg) intravenous zoledronic acid were given (must have received them >3 years before randomization)
- If a different intravenous bisphosphonate was given, if a dose of less than 5 mg of zoledronic acid was given, if intravenous dosing was off-schedule (not every 12 months) for zoledronic acid or another intravenous bisphosphonate, or if there was intermittent

compliance (stopping and starting) with oral bisphosphonate therapy, the PI will employ discretion in determining eligibility of the subject for the study.

- Use of denosumab (within the past 3 years or ≥ 3 injections ever)
- Oral glucocorticoid use (≥ 5 mg prednisone) taken within 3 months prior to enrollment
- Hypercalcemia (albumin-corrected serum [Ca] > 10.2 mg/dL), hypocalcemia (albumin-corrected serum [Ca] < 8.8 mg/dL), elevated intact PTH level, or hypercalciuria (urinary Ca > 300 mg/24 hours) at screening
- 25 OH vitamin D levels < 20 ng/ml or > 80 ng/ml at screening
- Estimated glomerular filtration rate < 30 ml/min (chronic kidney disease (CKD) stage 4 or 5)
- Cancer within past 5 years except for non-melanomatous skin cancers and except for cancers that have been deemed low risk or in remission by appropriate cancer-treating provider and stable for at least 3 years (e.g., noninvasive low grade primary papillary urothelial carcinoma or microcarcinoma of the thyroid such as papillary thyroid cancer)
- History of skeletal radiation, prior history of osteosarcoma or bone metastases
- Substance abuse (> 3 drinks/day), liver disease or impaired liver function (abnormal liver function tests defined as greater than 3 times the upper limit of normal), known cirrhosis, malabsorption
- Poorly controlled diabetes (A1c $\geq 9.0\%$) or current thiazolidinedione therapy
- Drugs metabolized through CYP2D6 (e.g., flecainide, tricyclic antidepressants) and strong inducers or inhibitors of CYP3A4 (e.g., itraconazole, ketoconazole)
- Testosterone therapy with dose change within last 12 months; or androgen deprivation therapy (ADT) within 12 months
- Thyrotropin (TSH) level < 0.01
- Congenital long QT syndrome, history of QT interval prolongation, family history of long QT syndrome or sudden cardiac death, and other conditions that predispose to QT interval prolongation and ventricular arrhythmia
- Hypersensitivity to teriparatide or any excipients in Forteo
- Use of other calcium-lowering drugs (e.g., calcitonin, bisphosphonates, denosumab)
- Moderate to severe hepatic impairment
- High risk for active urolithiasis, defined as having passed a kidney stone clinically within the last 5 years
- Upper gastrointestinal bleeding with a history of a clinical episode of upper gastrointestinal bleeding within the last 10 years that was not definitively treated by a surgical procedure
- Orthostatic hypotension or a known history of orthostatic hypotension documented in the chart or provided by the patient upon clinical history-taking
- Impaired cardiac function either diagnosed symptomatic heart failure or heart failure requiring medical therapy
- Average LS T-score by DXA $> +1.0$
- Underlying spinal disease such as diffuse idiopathic skeletal hyperostosis or Bastrup's disease

6.4 Additional Signoff for Randomization Eligibility

We will have the Co-Investigator of the study signoff on the eligibility for randomization of each subject which will involve a review of the lab tests, DXA scans, medical history and concomitant medications to assure a secondary check that the subject is eligible for randomization.

7 CONCURRENT MEDICATIONS

As medically appropriate, all subjects will be encouraged to continue the same medications throughout the entire study period, without introduction of new chronic therapies. Because new therapies will be medically necessary in some cases, participants will be queried throughout the study about changes to concomitant medications.

7.1 Allowed Medications and Treatments

Standard therapies are allowed, except for treatments noted in the exclusion criteria described above and as noted in “Prohibited Medications” below.

7.2 Prohibited Medications and Treatments

The following medications are prohibited during the study. Use of these at screening will make a participant ineligible to participate. Initiation during the trial will be considered a protocol violation.

- Osteoporosis drug therapy as follows
- Any osteoporosis drug therapy within 12 months; any prior course of TPTD for ≥ 3 months
- Prior oral bisphosphonate use: if duration of use is < 6 months (must have stopped use for ≥ 1 year before randomization); if duration of use is 6-24 months (must have stopped use for > 2 years before randomization); if duration of use is > 24 months (must have stopped use for > 3 years before randomization)
- Prior intravenous bisphosphonate use: if one dose (5 mg) intravenous zoledronic acid was given (must have received it > 2 years before randomization); if 2 or more doses (5 mg) intravenous zoledronic acid were given (must have received them > 3 years before randomization)
- Use of denosumab (within the past 3 years or ≥ 3 injections ever)
- Oral glucocorticoid use (≥ 5 mg prednisone) taken within 3 months prior to enrollment
- Current thiazolidinedione therapy
- Drugs metabolized through CYP2D6 (e.g., flecainide, tricyclic antidepressants, itraconazole, ketoconazole)
- Testosterone therapy with dose change within last 12 months; or androgen deprivation therapy (ADT) within 12 months

8 STUDY TREATMENTS

8.1 Method of Assigning Subjects to Treatment Groups

After eligibility is confirmed and a participant successfully completes the run-in period, he will be assigned to a treatment group (TPTD+cinacalcet or TPTD+PBO) using a block randomization scheme. Randomization numbers will be assigned in consecutive order at the randomization visits.

8.2 Blinding

Cinacalcet and placebo (PBO) tablets will be prepared and assigned randomization numbers by the investigational pharmacist at the SFVAHCS. Due to the objectives of the study, cinacalcet vs. PBO assignments will not be known to investigators, research staff, or participants, or others involved in outcome assessment. The following study procedures will be in place to ensure double-blind administration of study treatments and outcome ascertainment:

- Access to the randomization code will be strictly controlled.
- Packaging and labeling of cinacalcet and placebo tablets will be identical to maintain the blind.

The study blind will be broken on completion of the clinical study and after the study database has been locked. At that time, participants will be informed about their treatment group assignments.

During the study, the blind may be broken only in emergencies when knowledge of the patient's treatment group is necessary for further patient management. When possible, the Investigator should discuss the emergency with the Medical Monitor prior to emergency unblinding.

8.3 Formulation of Test and Control Products

8.3.1 FORMULATION OF TEST PRODUCT

Teriparatide (TPTD) will be purchased for this study by the SFVAMC Research Pharmacist and staff. It is produced by Lilly for clinical use, and the standard FDA-approved dispensing pen for this medication will be dispensed to subjects in the study.

Cinacalcet (30 mg tablets) will be purchased for this study by the SFVAMC Research Pharmacist and staff from Amgen. They are the producers of the medication which is an FDA-approved calcimimetic.

White tablets for the placebo which will contain no active ingredients will be purchased for the study from the Valor Pharmacy.

Calcium and vitamin D3 supplements will be purchased from reliable manufacturers by our Research Pharmacy.

All the study medications will be purchased and none will be formulated on site.

8.3.2 FORMULATION OF CONTROL PRODUCT

The placebo tablet that will be dispensed in a randomized manner against cinacalcet and will be purchased from Valor Pharmacy, a commercial manufacturer, by our Research Pharmacist for the trial. We will not be formulating it or reconstituting it on site.

8.3.3 PACKAGING AND LABELING

The study drugs and the study supplements will be dispensed by the SFVAMC outpatient research pharmacy under the supervision of Dr. Henry Leung. The packaging and labeling will reflect that all patients will receive teriparatide (TPTD) pens and either the cinacalcet vs placebo tablets (30 mg) that will be dispensed as the second study drug and all of the study team will be blinded to the assignment of the subject. Calcium supplements and vitamin D3 will be given at doses prescribed by the study physicians and will be labeled as per the Research Pharmacy procedure for each subject.

8.4 Supply of Study Drug at the Site and Dispensing to Participants

8.4.1 DOSAGE AND REGIMEN

All participants will be instructed to self-administer teriparatide 20 mcg SC daily. Participants will be instructed to swallow tablets of cinacalcet 30 mg or placebo by mouth once daily.

8.4.2 DISPENSING

The SFVAHCS investigational pharmacist will dispense the teriparatide and the cinacalcet or placebo upon receipt of prescriptions signed by a physician member of the study team.

8.4.3 ADMINISTRATION INSTRUCTIONS

At Screening Visit 2, a member of the study team will demonstrate the procedure for self-injection of teriparatide. At the Randomization Visit, that demonstration will be repeated. At the Randomization Visit, the initial dose of teriparatide and the initial dose of cinacalcet will be

administered, and the Pharmacodynamics Study (if performed) will follow. Subsequently, participants will take the teriparatide and the cinacalcet or placebo at home.

8.4.4 STORAGE

Study drug that has not been dispensed to participants will be stored securely within the SFVAHCS investigational pharmacy.

8.5 Study Drug Accountability

An accurate and current accounting of the dispensing and return of study drug for each subject will be maintained on an ongoing basis by a member of the study site staff. The number of study drug dispensed and returned by the subject will be recorded on the Investigational Drug Accountability Record. The study monitor will verify these documents throughout the course of the study.

8.6 Measures of Treatment Compliance, Daily Diary Calendar Log

Subjects will be asked to complete a daily diary calendar log documenting their adherence to the teriparatide (TPTD) and to the cinacalcet or placebo (PBO), and any adverse events. They will be asked to bring the diary calendar log to the follow-up study visits along with all unused study drug. This log will be used to assess compliance and encourage careful completion of the study drug and supplement administration.

8.7 Other Interventions

Supplements in the form of calcium citrate tablets (200 mg tablets) will be given in both treatment arms to subjects along with vitamin D3 (1,000 International Units) by mouth daily. Ca supplements will be adjusted along with an assessment of dietary Ca intake to reach a total of ~1,000 mg elemental Ca per day. If 25OH vitamin D level rises to >80 ng/mL, then the study physician will instruct the participant in decreasing his vitamin D supplement dose.

9 STUDY PROCEDURES AND GUIDELINES

A Schedule of Events representing the required testing procedures to be performed for the duration of the study is diagrammed in Section 10 and Appendix 1.

Prior to conducting any study-related activities, written informed consent and the Health Insurance Portability and Accountability Act (HIPAA) authorization must be signed and dated by the subject. If appropriate, assent must also be obtained prior to conducting any study-related activities.

9.1 Clinical Assessments

Data for the following outcomes will be collected at the VA or UCSF Clinical Research Center (CRC) during screening interviews and examinations or by self-administered questionnaire.

9.1.1 DEMOGRAPHICS

Demographic information (date of birth, gender, race) will be recorded at Screening Visit 1.

9.1.2 MEDICAL HISTORY

Relevant medical history, including history of current disease and information regarding underlying diseases will be recorded during initial screening and at Screening Visits 1 and 2.

9.1.3 CALCIUM AND OTHER NUTRIENT DIETARY INTAKE

Comprehensive dietary intakes will be assessed using the Block Food Frequency Questionnaire for all enrolled subjects during the Screening Visit 2 and at the final Week 48/Month 11 Study Visit. Calcium and vitamin D intake will be estimated by a standardized screener at Screening Visit 2 in order to determine the individual calcium supplement dose necessary to reach the total calcium intake goal of 1000 mg/d, and calcium dietary and supplement intake will be discussed at each study visit.

9.1.4 CHECK OF VITAL SIGNS

These are standard clinical measurements for safety and patient well-being and will be checked at every face to face encounter with the subjects (to include pulse, blood pressure, respirations, and weight).

9.1.5 ADHERENCE AND ACCEPTABILITY AND DAILY DIARY CALENDAR LOG

Treatment adherence will be assessed at all telephone and in-person study visits with the subjects by inquiring about the consistency of medication taking and supplement use along with adverse events and by review of the daily diary calendar log, which the subject will bring to all appointments.

9.1.6 BLOOD AND URINE COLLECTIONS

See also “Research Laboratory Testing,” below. Blood will be drawn at Screening Visit 2, Randomization Visit, and all subsequent in-person study visits through the end of the study at Week 48/Month 11 (study visits at 1, 2, 3, 5, 6, 9, and 11 months or Weeks 4, 8, 12, 20, 24, 36, 48 and at the Week 1/Telephone Visit and optional in-person visit); see Appendix for details). Participants will perform 24-hour urine collections at baseline at Screening Visit 2 and Randomization and at Study Visits at 1, 2, 3, 6, 9, and 11 months (or Weeks 4, 8, 12, 20, 24, 36, 48).

9.1.7 CONCOMITANT MEDICATIONS

All concomitant medication and concurrent therapies will be documented at Screening Visit 2, with discussion and updates at all subsequent study visits. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

9.1.8 BMD AND TBS (TRABECULAR BONE SCORE)

At baseline at Screening Visit 1 and at Week 48/Month 11 at the end of the study, we will measure areal BMD at the lumbar spine, proximal femur, and radius using DXA (Horizon A, Hologic). With DXA, we will also obtain the TBS at both time-points.

9.1.9 ADVERSE EVENTS

Adverse events (AEs) will be recorded at each study contact or when otherwise volunteered by the subject. (See also “Adverse Event Assessment and Reporting.”)

9.2 Clinical Laboratory Measurements

9.2.1 REAL-TIME LABORATORY TESTING

See also “Blood and Urine Collection” above. As it is collected, blood will be sent to the San Francisco VAMC Clinical Lab for determination of a comprehensive metabolic panel including serum calcium, albumin, creatinine, and glucose, PTH, phosphate, 25 OH vitamin D, hemoglobin A1c, and complete blood count (depending on the visit), as well as thyrotropin (TSH) for determination of eligibility. Urine from 24-hour collections will be sent to the San Francisco VAMC Clinical Lab for determination of urinary calcium, sodium, and creatinine levels at the specified visits (see Appendix 1).

9.2.2 RESEARCH LABORATORY TESTING

Serum will be frozen at -80 C until batch analyzed for biochemical markers of bone turnover and other hormone measurements (at Randomization and Months 1, 2, 3, 5, 6, 9, 11 or Weeks 4, 8, 12, 20, 24, 36, 48). Serum P1NP (a study endpoint) is one key marker that will be measured. As exploratory endpoints, we plan to assess the bone turnover markers serum C-telopeptide (CTX), bone specific alkaline phosphatase, and osteocalcin, as well as the bone turnover/osteoclast and osteoblast regulators including osteoprotegerin (OPG), receptor activator of nuclear factor kappa B ligand (RANK-L), and sclerostin. As an outcome of parathyroid hormone (PTH) action, we will also assess serum 1,25(OH)₂ vitamin D. Other serum and urine will be frozen for future analyses and to confirm any findings if needed.

9.2.3 COLLECTION, STORAGE AND ANALYSIS OF PERIPHERAL BLOOD MONONUCLEAR CELLS (PBMCs)

We will obtain PBMCs from the blood samples collected at baseline at Randomization Visit/Day 1 and the post-treatment at Study Visits (Months 1, 2, 3, 6, 9, and 11 or or Weeks 4, 8, 12, 20, 24, 36, and 48) in both study arms for exploratory studies. Fluorescence activation cell sorting (FACS) analyses will be done to separate different cell populations anticipated to increase with administration of PTH (1-34) or PTH (1-84) based on prior studies (1-6). Those populations include circulating osteogenic precursors (cOP), which can be obtained by sorting for osteocalcin+, alkaline phosphatase+, CD15- (granulocyte marker), and/or lin- (hematopoietic lineage), and further defined by early OB (osteoblast) markers (CD34+ and CD146+). Gene profiling for known OB markers (e.g., *Runx2*, *alk phos*, *osterix*, *c-fos*, *osteocalcin* etc) will be done on mRNA (messenger RNA) from cell populations by qPCR (quantitative polymerase chain reaction) in the laboratory. This would support the phenotype as OB lineage cells. For circulating osteoclast precursor quantification, PBMCs from subjects in both 2 treatment arms at specific time-points will be cultured in the presence of receptor activator of nuclear kappa B ligand (RANK-L), stained for tartrate-resistant alkaline phosphatase, and counted (6). Techniques for doing these studies (FACS, cell culture, qPCR) are familiar to both Dr. Shoback, the PI, and Drs. Wenhan Chang and Mary Nakamura, study collaborators. These detailed exploratory analyses will be performed on a subset of study subjects.

9.2.4 PHARMACODYNAMIC (PD) TESTING

At the Randomization Visit, 24/48 men will have PD assessments made after an indwelling venous catheter is placed for blood samplings (unless, at the discretion of the Principal Investigator decides it is an undue burden for one of the 24 out of 48 men to partake in an 8 hour visit). Serum calcium, albumin, and PTH will be obtained at time 0, 1, 2, 4, and 8 hours after administering teriparatide (20 ug) by subcutaneous injection and cinacalcet (30 mg) or placebo orally. Subjects will be monitored for AEs during the procedure. Serum calcium values will be analyzed by the SFVAMC Clinical Chemistry Lab on the day of the study. Intact PTH levels will be batch-analyzed at the end of study.

9.2.5 SPECIMEN BANKING

With explicit informed consent, serum and urine will also be banked for possible future analyses.

References for Section 9

1. Drake MT, Srinivasan B, Mödder UI et al: Effects of intermittent parathyroid hormone treatment on osteoprogenitor cells in postmenopausal women. *Bone* 49:349-55, 2011.
2. Yu E, Kumbhani R, Siwila-Sackman E et al: Teriparatide (PTH1-34) increases peripheral hematopoietic stem cells in postmenopausal women. *J Bone Min Res* 29:1380-6, 2014.

3. D'Amelio P, Tamone C, Sassi F et al: Teriparatide increases the maturation of circulating osteoblast precursors. *Osteo Int* 23: 1245-53, 2012.
4. Rubin MR, Manavalan JS, Dempster DW et al: Parathyroid hormone stimulated circulating osteogenic cells in hypoparathyroidism. *J Clin Endo Metab* 96: 176-186, 2011.
5. Manavalan JS, Cremers S, Dempster DW et al: Circulating osteogenic precursor cells in type 2 diabetes mellitus. *J Clin Endo Metab* 97: 3240-50, 2012.
6. Rubin MR, Manavalan JS, Agarwal JS et al: Effects of rosiglitazone vs metformin on circulating osteoclast and osteogenic precursor cells in postmenopausal women with type 2 diabetes mellitus. *J Clin Endo Metab* 99: E1933-E1942, 2014.

10 EVALUATIONS BY VISIT

10.1 Screening Visit 1

- Screen for eligibility
- Review the study with the subject and obtain written informed consent and HIPAA authorizations
- Assign the subject a unique screening number
- DXA spine, hip, radius
- Dispensing of materials to be used subsequently for 24-hour urine collection at home
- Remind subject of the date and time of the next visit

10.2 Screening Visit 2

(Flexible timing, to follow Screening Visit (SV) 1. SV1 and SV2 may occur on the same day at the investigator's discretion, based on the participant's ability to make multiple trips to San Francisco and based on availability of phlebotomy.)

- Medical history
- Vital signs
- Physical exam
- Food frequency questionnaire
- Screening laboratory tests: blood draw
- Screening laboratory tests: Submission of 24-hour urine collection
- Record concomitant medications
- Demonstration of teriparatide injection
- Assessment of AEs
- Calcium/vitamin D intake check
- Dispensing of calcium and vitamin D supplements to begin the 4-week supplement run-in period
- Dispensing of materials to be used subsequently for 24-hour urine collection at home
- Dispensing of daily diary calendar log for the subject to complete and bring to the next and subsequent appointments and training and orientation of subject in filling it out
- Remind subject of the date and time of the next visit

10.3 Randomization Visit

(4 weeks after Screening Visit 2 and after completion of 4 week run-in period taking calcium and vitamin D3 supplements. Window opens 3 weeks after and closes 8 weeks after Screening Visit 2.)

- Vital signs
- Submission of 24-hour urine collection
- Record concomitant medications
- Demonstration of teriparatide injection

- Administration of initial dose of teriparatide and initial dose of cinacalcet or placebo
- Pharmacodynamic study: Blood draws at 0, 1, 2, 4, and 8 hours after med administration
- Banking of blood
- PBMC isolation (if being done)
- Assessment of AEs
- Calcium/vitamin D intake check
- Dispensing of teriparatide and of cinacalcet or placebo
- Dispensing of calcium and vitamin D supplements
- Dispensing of materials to be used subsequently for 24-hour urine collection at home
- Review of daily diary calendar log records (supplements)
- Remind subject of the date and time of the next visit and not to take study medications on the morning of the visit

10.4 Week 1 Visit (Labs + Telephone Visit + optional in-person visit with study staff)*

(One week after Randomization Visit. Window opens 5 days after and closes 2 weeks after Randomization Visit.)

- Phlebotomy
- Record concomitant medications
- Assessment of AEs
- Calcium/vitamin D intake check
- Discussion of any difficulties with injection pen device
- Remind subject of the date and time of the next visit and not to take study medications on the morning of the visit
- *Optional in-person visit with study staff will in general occur unless for geographic reasons the in-person visit is substituted for a telephone call and lab visit at a community-based outpatient clinic

10.5 Week 4 or ~Month 1 Visit

(One month after Randomization Visit. Window opens 3 weeks after and closes 7 weeks after Randomization Visit.)

- Vital signs
- Submission of 24-hour urine collection
- Record concomitant medications
- Phlebotomy
- Banking of blood
- PBMC isolation (if being done)
- Assessment of AEs
- Calcium/vitamin D intake check
- Dispensing of teriparatide and of cinacalcet or placebo
- Dispensing of calcium and vitamin D supplements
- Dispensing of materials to be used subsequently for 24-hour urine collection at home
- Review of daily diary calendar log records (study medications and supplements)
- Remind subject of the date and time of the next visit and not to take study medications on the morning of the visit and come to the clinic fasting

10.6 Week 8 or ~Month 2 Visit

(Two months after Randomization Visit. Window opens 6 weeks after and closes 10 weeks after Randomization Visit.)

- Vital signs

- Submission of 24-hour urine collection
- Record concomitant medications
- Phlebotomy
- Banking of blood
- PBMC isolation (if being done)
- Assessment of AEs
- Calcium/vitamin D intake check
- Dispensing of teriparatide and of cinacalcet or placebo
- Dispensing of calcium and vitamin D supplements
- Dispensing of materials to be used subsequently for 24-hour urine collection at home
- Review of daily diary calendar log records (study medications and supplements)
- Remind subject of the date and time of the next visit and not to take study medications on the morning of the visit and come to the clinic fasting

10.7 Week 12 or ~Month 3 Visit

(Three months after Randomization Visit. Window opens 10 weeks after and closes 16 weeks after Randomization Visit.)

- Vital signs
- Submission of 24-hour urine collection
- Record concomitant medications
- Phlebotomy
- Banking of blood
- PBMC isolation (if being done)
- Assessment of AEs
- Calcium/vitamin D intake check
- Dispensing of teriparatide and of cinacalcet or placebo
- Dispensing of calcium and vitamin D supplements
- Review of daily diary calendar log records (study medications and supplements)
- Remind subject of the date and time of the next visit and not to take study medications on the morning of the visit and come to the clinic fasting

10.8 Week 20 or ~Month 5 Visit

(Five months after Randomization Visit. Window opens 4 months after and closes 6 months after Randomization Visit.)

- Vital signs
- Record concomitant medications
- Phlebotomy
- Banking of blood
- Assessment of AEs
- Calcium/vitamin D intake check
- Dispensing of teriparatide and of cinacalcet or placebo
- Dispensing of calcium and vitamin D supplements
- Dispensing of materials to be used subsequently for 24-hour urine collection at home
- Review of daily diary calendar log records (study medications and supplements)
- Remind subject of the date and time of the next visit and not to take study medications on the morning of the visit and come to the clinic fasting

10.9 Week 24 or ~Month 6 Visit

(Six months after Randomization Visit. Window opens 5 months after and closes 7 months after Randomization Visit.)

- Vital signs
- Submission of 24-hour urine collection
- Record concomitant medications
- Phlebotomy
- Banking of blood
- PBMC isolation (if being done)
- Assessment of AEs
- Calcium/vitamin D intake check
- Dispensing of teriparatide and of cinacalcet or placebo
- Dispensing of calcium and vitamin D supplements
- Dispensing of materials to be used subsequently for 24-hour urine collection at home
- Review of daily diary calendar log records (study medications and supplements)
- Remind subject of the date and time of the next visit and not to take study medications on the morning of the visit and come to the clinic fasting

10.10 Week 36 or ~Month 9 Visit

(Nine months after Randomization Visit. Window opens 8 months after and closes 10 months after Randomization Visit.)

- Vital signs
- Submission of 24-hour urine collection
- Record concomitant medications
- Phlebotomy
- Banking of blood
- PBMC isolation (if being done)
- Assessment of AEs
- Calcium/vitamin D intake check
- Dispensing of teriparatide and of cinacalcet or placebo
- Dispensing of calcium and vitamin D supplements
- Dispensing of materials to be used subsequently for 24-hour urine collection at home
- Review of daily diary calendar log records (study medications and supplements)
- Remind subject of the date and time of the next visit and not to take study medications on the morning of the visit and come to the clinic fasting

10.11 Week 48 or ~Month 11 Visit

(Eleven months after Randomization Visit. Window opens 10 months after and closes 12 months after Randomization Visit.)

- DXA spine, hip, forearm
- Vital signs
- Physical exam
- Submission of 24-hour urine collection
- Record concomitant medications
- Administration of Food Frequency Questionnaire
- Phlebotomy
- Banking of blood
- PBMC isolation (if being done)
- Assessment of AEs
- Calcium/vitamin D intake check
- Collection of unused study medications
- Review and turning in of daily diary calendar log records (study medications and supplements)

11 ADVERSE EVENT ASSESSMENT AND REPORTING

11.1 Adverse Events

There will be continuous safety surveillance of participants. According to the 1996 International Conference on harmonization E6 Guidelines for Good Clinical Practice, an adverse event (AE) is defined as an untoward or unfavorable medical occurrence in a human participant, including any abnormal sign, symptom, or disease, temporally associated with participation in the research, whether or not considered related to participation in the research.

- AEs will be recorded in a systematic manner at every study visit and when otherwise volunteered by the participant. A standardized AE form will be used for recording the pertinent details.
- At the time a participant describes an AE to a study team member, the study team member may advise the participant to seek medical care, if appropriate. If the study team member is not a physician, he or she will contact the PI or another study physician to determine the best advice to provide the participant.
- AEs will be classified as expected or unexpected. An expected AE is an AE that may be reasonably anticipated to occur as a result of the study procedures or study participation and is thus described in the informed consent document. An AE will be defined as unexpected if it is not described or exceeds the nature, severity, or frequency described in the informed consent document and current IRB application.

11.1.1 AE SEVERITY

The National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0 should be used to assess and grade AE severity, including laboratory abnormalities judged to be clinically significant. If the experience is not covered in the modified criteria, the guidelines shown in Table 1 below should be used to grade severity. It should be pointed out that the term "severe" is a measure of intensity and that a severe AE is not necessarily serious.

Table 1. AE Severity Grading

Severity (Toxicity Grade)	Description
Mild (1)	Transient or mild discomfort; no limitation in activity; no medical intervention or therapy required. The subject may be aware of the sign or symptom but tolerates it reasonably well.
Moderate (2)	Mild to moderate limitation in activity, no or minimal medical intervention/therapy required.
Severe (3)	Marked limitation in activity, medical intervention/therapy required, hospitalizations possible. (See below for details.)
Life-threatening (4)	The subject is at risk of death due to the adverse experience as it occurred. This does not refer to an experience that hypothetically might have caused death if it were more severe.

An AE is a serious adverse event (SAE) if it results in any of the following outcomes:

- Death

- Life-threatening adverse experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant disability/incapacity
- Congenital anomaly/birth defect or cancer
- Any other experience suggesting a significant hazard, contraindication, side effect or precaution that may require medical or surgical intervention to prevent one of the outcomes listed above
- Event that changes the risk/benefit ratio of the study

11.1.2 AE RELATIONSHIP TO STUDY PARTICIPATION

Cause will be determined for all AEs. The PI will assess AE causality in terms of overall study participation and determine whether an AE is thought to be related to the intervention or any study-related activity.

The following definitions, provided by the UCSF IRB, will be used to assess the AE relationship to study participation:

- **Definitely Related**: An AE is definitely related to study participation if it is clear that the event was caused by study participation. A definitely related event has a strong temporal relationship and an alternative cause is unlikely.
- **Probably Related**: An AE is probably related when there is a reasonable possibility that the event is likely to have been caused by study participation. The AE has a timely relationship to the study procedure(s) and follows a known pattern of response, but a potential alternative cause may be present.
- **Possibly Related**: An AE is possibly related when there is a reasonable possibility that the event might have been caused by study participation. A possibly related event may follow no known pattern of response and an alternative cause seems more likely. In other circumstances there may be significant uncertainty about the cause of the event, or a possible relationship to study participation cannot reasonably be ruled out.
- **Unrelated**: The cause of the AE is known and the event is in no way related to any aspect of study participation. If there is any uncertainty regarding AE causality then the event must be assessed as possibly related to research participation and reported to the IRB as indicated. Often, the cause of an unrelated AE is disease progression.

Additional guidance is offered in Table 2:

Table 2. AE Relationship to Study Drug

Relationship to Drug	Comment
Definitely	Previously known toxicity of agent; or an event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is not explained by any other reasonable hypothesis.
Probably	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to the suspected drug; that is confirmed by stopping or reducing the dosage of the drug; and that is unlikely to be explained by the known characteristics of the subject's clinical state or by other interventions.

Possibly	An event that follows a reasonable temporal sequence from administration of the drug; that follows a known or expected response pattern to that suspected drug; but that could readily have been produced by a number of other factors.
Unrelated	An event that can be determined with certainty to have no relationship to the study drug.

11.2 Adverse Event Reporting

The PI will be responsible for the reporting of AEs to the UCSF Institutional Review Board (IRB) and to the VA CSR&D Data Monitoring Committee according to their rules and regulations. The IRB will review any submitted reports to determine whether an event meets the definition of an Unanticipated Problem involving risks to participants or other (UP). (A UP may be an AE, although the majority of AEs are not UPs. A UP may also be another incident or outcome that suggests that the research in question places participants or others at a greater risk of harm than was previously known or recognized.) The IRB is required to report all UPs to the Department of Health and Human Services (DHHS) Office for Human Research Protection, appropriate University and affiliate officials, and study sponsors. In addition, because of the involvement and sponsorship of the VA for this study, the San Francisco VA Health Care System is required to report to the Office of Research Oversight (ORO) any situations that are reportable under VHA Handbook 1058.01.

- Within 5 working days of her awareness, the PI will report to the IRB any AEs determined to be definitely, probably, or possibly related AND Serious or Unexpected.
- Within 5 working days of her awareness, the PI will report to the IRB any Major Violation of protocol (including but not limited to enrollment of ineligible participant), any need for immediate protocol change to protect participant safety, and any Major Incident (including but not limited to a significant complaint or concern, lapse in study approval, or breach of confidentiality).

Study sites will document all SAEs that occur (whether or not related to study drug) per UCSF IRB guidelines. The collection period for all SAEs will begin after informed consent is obtained and end after procedures for the final study visit have been completed.

In accordance with the standard operating procedures and policies of the local IRB/Independent Ethics Committee (IEC) and the Department of Veterans Affairs, the sponsor of this trial, the principal investigator will report SAEs to the IRB/IEC and to the VA CSR&D Data Monitoring Committee as described in Section 11.3).

11.3 Safety Review Plan, Medical Monitor, Data Monitoring Committee

11.3.1 MEDICAL MONITOR

11.3.1.1 SELECTION OF THE MEDICAL MONITOR

The PI has appointed Dr. Tiffany Kim the Medical Monitor on site for this clinical trial. Dr. Kim is highly qualified to fulfill this role as a board-certified endocrinologist and physician at the SFVAHCS and UCSF as someone not a member of the study team. She will receive no funds for serving as Medical Monitor.

11.3.1.2 SCHEDULE OF MEETINGS WITH MEDICAL MONITOR

The Medical Monitor will review lab data looking for any serum calcium and albumin levels or urinary calcium and creatinine levels that would be cause for concern in the regular conduct of the trial. The PI and other members of the study team will meet with the monitor at the beginning of the trial and then every 2-4 weeks or as needed, to review the conduct of the trial, any AEs that may arise, and any protocol deviations that might occur.

11.3.1.3 BLINDING OF REPORTS

At any regular meetings of the study team with the Medical Monitor, AEs and other data presented to the Medical Monitor will be blinded to treatment group assignment. If the Medical Monitor has any concerns about patterns of AEs or protocol violations, then she will discuss these concerns with the PI, who will discuss them with the IRB and the VA CSR&D Data Monitoring Committee.

11.3.2 DATA SAFETY MONITORING COMMITTEE (DMC)**11.3.2.1 COMPOSITION AND EXPERTISE**

The VA Clinical Sciences Research and Development (CSR&D) Centralized Data Monitoring Committee (DMC) for Medical and Surgical Protocols of the US Department of Veterans Affairs has a membership of 19 professionals that do all the Department of Veterans Affairs clinical trial safety monitoring in a highly organized manner. Many of those 19 members of the centralized committee are experienced clinical researchers within the VA system as well as biostatistics experts and physicians.

Oversight for this trial will be done by a primary reviewer, a secondary reviewer and a biostatistician selected by the CSR&D Centralized DMC and already assigned to the study.

11.3.2.2 CHARGE, RESPONSIBILITIES, AND GUIDANCE

The DMC is charged with the following responsibilities toward safety monitoring for the trial by the charter, which is included with the study documents as an attachment. From "CSR&D Data Monitoring Committee Guidance, Version 1.3, 9/2/15":

The CSR&D DMC is primarily responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of trial interventions and monitoring the progress of assigned clinical trials under review. The DMC conducts comprehensive reviews of each study at each meeting, unless otherwise specified by the DMC. Recruitment is be monitored according to a schedule set by the DMC. Additionally, the DMC may also make recommendations relating to selection, recruitment and retention of research subjects; patient management; data management; and quality control. The DMC will not evaluate the scientific merit, methodology or overall design, and budgetary constraints of an Institutional Review Board (IRB) approved protocol under review, except where changes to the protocol may result in a change in safety level or monitoring. The CSR&D DMC is advisory to the Director of CSR&D.

11.3.2.3 FREQUENCY AND SCHEDULE OF MEETINGS FOR TRIAL MONITORING

The Department of Veterans Affairs Centralized DMC meets three times a year to review proposals and reports, and evaluate proposed significant modifications to existing proposals. The DMC usually meets twice a year via conference call and for its fall meeting convenes in

person at Edward Hines, Jr. VA Hospital. DMC monitoring of a study starts with an initial review and continues through the end of the follow-up period. The PI submits progress reports through the accrual period. After accrual has ended, the PI continues to report SAEs to the DMC until the follow-up period has ended.

11.3.2.4 DATA THE DMC WILL REVIEW, REPORTING OF SERIOUS ADVERSE EVENTS (SAEs)

The DMC will request the Principal Investigator to submit progress reports 3 times a year--April 1, August 1 and December 1. The progress report is submitted in a 3-page template format (see attachment with study documents). The DMC will also ask the PI to report SAEs within 48 hours of becoming aware of the event. The template for the SAE report is attached with the study documents.

11.3.2.5 PROCEDURE FOR EMERGENCY UNBLINDING

The Department of Veterans Affairs DMC Office can request from the DMC Chair an emergency meeting of the DMC when it receives information, either external or internal to the study, indicating significant new risks to study patients may be present. Such information could include new safety information from sources such as the Food and Drug Administration, one or more concerning SAE reports within the study, or other changes in the study that may represent a significant new risk to study patients. The study team will work closely with the DMC related to any of these safety concerns.

11.3.2.6 RULES FOR TERMINATION OF PARTICIPATION

Based on DMC review of progress reports and other communication with the Principal Investigator, the DMC has the authority to recommend to the Director of CSR&D, study continuation unconditionally or conditionally; probation or release from probation; or termination. Probation is most often recommended due to under-enrollment. For studies that subsequently do not meet the terms of the probation, the DMC may recommend early termination.

11.3.2.7 DMC CHARTER

Each study monitored by the DMC will also have its own specific charter after it has begun enrollment. Attached to the materials in the application to the IRB is a template for this charter as one of the attachments and the currently active Charter for the study.

11.3.3 REASSESSMENT OF RISK – BENEFIT RATIO

At every meeting of the VA CSR&D DMC for this study, the DMC will determine (1) if the risk/benefit ratio for study participation continues to be acceptable; (2) if the research protocol and informed consent document accurately and completely present risk information to research subjects; and (3) whether subjects already enrolled should be advised of newly identified risks.

11.3.4 EMERGENCY UNBLINDING FOR THE TRIAL

In the event of a clinical emergency, a participant will be assumed to be taking active cinacalcet. On an emergency basis (only), the blind could be broken and a participant and/or treating clinician could be informed of cinacalcet vs. placebo assignment.

11.3.5 TERMINATION OF PARTICIPATION

Participants may voluntarily withdraw from study participation at any time. Also, if the PI, Medical Monitor, or DMC determines that further participation in the study or in a particular study procedure may be detrimental to the participant's health or well-being, then participation in

the study will be discontinued.

11.3.6 STOPPING CRITERIA

In theory, the PI or the Department of Veterans Affairs could elect to stop the trial early, if harm is clearly demonstrated, benefit is clearly demonstrated, or it is determined that it will not be possible to accomplish the study aims. However, given the modest size and duration of the trial and the active comparator study arm, it is unlikely that such stopping criteria would be met.

11.3.7 CONTACT INFORMATION

Dr. Dolores Shoback should be contacted directly at these numbers to report medical concerns or questions regarding safety.

Telephone: (415) 221-4810 x 23336 (SFVAMC office)
(415) 575-0552 (VA Mission Bay office)

E-mails: dolores.shoback@ucsf.edu
dolores.shoback@va.gov

12 DISCONTINUATION AND REPLACEMENT OF SUBJECTS

12.1 Early Discontinuation of Study Drug

A subject may be discontinued from study treatment at any time if the subject, the investigator, Medical Monitor, or the Sponsor (Department of Veterans Affairs) feels that it is not in the subject's best interest to continue. The following is a list of possible reasons for study treatment discontinuation:

- Subject withdrawal of consent (or assent)
- Subject is not compliant with study procedures
- Adverse event that in the opinion of the investigator would be in the best interest of the subject to discontinue study treatment
- Protocol violation requiring discontinuation of study treatment
- Lost to follow-up
- Sponsor request for early termination of study

If a subject is withdrawn from treatment due to an adverse event, the subject will be followed and treated by the Investigator until the abnormal parameter or symptom has resolved or stabilized.

All subjects who discontinue study treatment should come in for an early discontinuation visit as soon as possible and then should be encouraged to complete all remaining scheduled visits and procedures.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

12.2 Withdrawal of Subjects from the Study

A subject may be withdrawn from the study at any time if the subject, the investigator, or the Sponsor (Department of Veterans Affairs) feels that it is not in the subject's best interest to continue.

All subjects are free to withdraw from participation at any time, for any reason, specified or unspecified, and without prejudice.

Reasonable attempts will be made by the investigator to provide a reason for subject withdrawals. The reason for the subject's withdrawal from the study will be specified in the subject's source documents.

If a participant decides to withdraw entirely from the study after taking at least 1 month of study drug, he will be encouraged to attend an Early Termination study visit with a DXA scan performed at that time.

12.3 Replacement of Subjects

If a subject withdraws from the study treatment during the first 4 weeks of the intervention period (i.e., within 8 weeks after the Randomization Visit), the Investigators may opt to replace him by randomizing an additional subject.

13 PROTOCOL VIOLATIONS

A protocol violation occurs when the subject, investigator, or Sponsor fails to adhere to significant protocol requirements affecting the inclusion, exclusion, subject safety and primary endpoint criteria. Protocol violations for this study include, but are not limited to, the following:

- Failure to meet inclusion/exclusion criteria
- Use of a prohibited concomitant medication

Failure to comply with Good Clinical Practice (GCP) guidelines will also result in a protocol violation. The Sponsor will determine if a protocol violation will result in withdrawal of a subject.

When a protocol violation occurs, it will be discussed with the investigator and a Protocol Violation Form detailing the violation will be generated. This form will be signed by a Sponsor representative and the Investigator. A copy of the form will be filed in the site's regulatory binder and in the Sponsor's files.

14 STATISTICAL METHODS AND CONSIDERATIONS

Prior to the analysis of the final study data, a detailed Statistical Analysis Plan (SAP) will be written describing all analyses that will be performed. The SAP will contain any modifications to the analysis plan described below.

14.1 General Considerations

Statistics will include descriptive as well as analytic approaches. We will use an intention-to-treat (ITT) approach, with all randomized men included in the analysis. We will attempt to collect complete follow-up data on every randomized subject, regardless of adherence. 2° per-protocol analyses will be done, limited to those who remained on medication and those with complete data. All statistical testing will be performed at nominal 0.05 level without adjustments for multiple comparisons.

14.2 Analysis of Primary Endpoint

To determine the effects of 11 months of treatment with TPTD+cinacalcet compared to TPTD+PBO on LS BMD (primary endpoint)

Testing the 1^o hypothesis for the effect of the 2 treatment arms on the % change in LS BMD will use a t-test with a two-sided significance level of 0.05. The extent of missing data will be reported in all statistical analyses. Overall missing data rates are expected to be low since we will make every attempt to obtain BMDs at 11 months for all men, regardless of medication use. 1^o analyses will be unadjusted. We will consider performing 2^o covariate-adjusted analyses if (by chance alone) any important co-variables (e.g., age, BMD, etc.) differ substantially ($p < 0.05$) at baseline.

Using standard statistical methods and means and SDs from published TPTD studies, we calculated the effect size (true difference in means between treatment groups) that can be detected based on a t-test comparison between treatment groups of the change in LS BMD with a fixed sample size of 24/group. Even if 20% of our subjects were lost to follow-up and did not contribute 11-month LS BMD data, with a sample size of 40 we would be powered to detect a between-group difference as small as 4.0%. A difference between treatment regimens of ~4% (e.g., mean LS BMD increase in TPTD+PBO of 5% vs 9% increase in the combination group) would be an effect size for BMD in the range that would be clinically promising and support pursuing further studies of this combination therapy for osteoporosis.

14.3 Analysis of Secondary Endpoints

To determine the effects of 11 months of treatment with TPTD+cinacalcet compared to TPTD+PBO on FN BMD and levels of the bone formation marker P1NP (secondary endpoints).

A similar approach will be taken for FN BMD and for the logarithm of the P1NP change as will be taken for the primary endpoint above. On an exploratory basis, changes in TBS from baseline to study end will be analyzed as BMD is. All hypotheses will be tested at the nominal 0.05 2-sided significance level, with no formal adjustment for multiple comparisons. In the analysis of 2^o outcomes and in other 2^o analyses, we recognize that this might increase type 1 error rates, due to multiple testing. To alleviate that concern, we will clearly distinguish 1^o from 2^o endpoints as well as exploratory analyses, look for consistency among multiple endpoints, and be cautious in our interpretation of marginally significant findings, particularly unexpected results not motivated by *a priori* hypotheses. The extent of missing data will be reported in all statistical analyses. Overall missing data rates are expected to be low since we will make every attempt to obtain BMDs at 11 months and P1NP at 3 months for all men, regardless of medication use. 1^o analyses will be unadjusted. We will consider performing 2^o covariate-adjusted analyses if (by chance alone) any important co-variables (e.g., age, BMD, etc.) differ substantially ($p < 0.05$) at baseline.

We will have 80% power (with an $\alpha = 0.05$) to detect a between-group difference in change in FN BMD as small as 3.5%. Since effects of TPTD on FN BMD in short-term studies are small, we recognize that +3.5% may be an ambitious difference between treatments for hip BMD. However, the point estimates may give us an indication of whether the combination has superior effects on BMD at the hip and help us plan future studies of this combination.

The distribution of P1NP change is non-Gaussian in multiple studies, requiring log transformation (log ratio) and back-transformation for presentation. Using data from PaTH trial of the 3-month change in P1NP, the back-transformed mean change (95% CI) was +148% (117%, 183%). Based on the SD of the log ratio in PaTH, a sample size of 40 (20/group, assuming 20% non-completers) will provide 80% power with $\alpha = 0.05$ to detect a difference of +137% (e.g., an increase from 148% to 285%) between P1NP responses of men treated with TPTD+cinacalcet vs TPTD+PBO.

To determine pharmacodynamic (PD) responses to TPTD+cinacalcet and to TPTD+PBO treatment in men with low bone mass. To establish physiologic response and confirm parameters of combination therapy, we will assess: (a) acute and chronic changes in the serum [Ca] and plasma intact PTH after drug administration; and (b) changes in urinary Ca excretion with both treatment regimens.

Serum and urinary Ca are key safety parameters. Effects will be assessed in several ways. For the 24 men who have the 8-hour PD testing with drug administration at the Randomization Visit, we will plot mean and standard deviation (SD) of acute change in serum [Ca] from pre-dose to post-dose over 2, 4 and 8 hours. However, our main safety endpoint will be the proportion in each treatment group who decrease to >5% below the lower limit of normal at 8 hours after dosing. We will compare the proportions between groups using a chi square test. Because all subjects will be receiving TPTD, which increases serum [Ca], we do not expect anyone will cross this threshold, but given that cinacalcet lowers serum [Ca], this safety endpoint will be important to assess. We will also compare the 2-, 4-, and 8-hour changes between groups using a t-test. We will also examine, in all 48 men, the mean serum [Ca] and PTH chronic changes from baseline to 1, 2, 3, 6, 9, and 11 months of treatment and test the null hypothesis (using a t-test) that there is no difference between treatment groups at for any time period. However, a difference in serum [Ca] change has little clinical meaning provided the values remain within normal range. Urinary Ca will be measured (pre-dose) at baseline and at 1, 3, 6, 9, and 11 months. We will compare the proportions of subjects in each treatment group with 24-hour urinary Ca >350 mg. We hypothesize that few subjects will cross this threshold, and that this will not vary by treatment. We will also consider change in 24-hour urinary Ca as a continuous endpoint, but this has little meaning clinically provided the values remain within normal range.

A sample size of 40 (20/group, assuming 20% non-completers) will provide 80% power with alpha=0.05 to detect a between-group difference of approximately 0.43 in the proportion of subjects who cross the threshold of serum Ca >5% below the lower limit of normal or of 24-hour urine Ca > 350 mg. Statistical power is thus limited, but we expect that no subjects will cross the serum Ca threshold and would consider such a result very reassuring. Likewise, we would be reassured by only a small number of subjects with hypercalciuria. The observation of a few subjects with large response would prompt study of the specific characteristics of those subjects.

15 DATA COLLECTION, RETENTION, AND MONITORING

15.1 Data Collection Instruments

The Investigator will prepare and maintain adequate and accurate source documents designed to record all observations and other pertinent data for each subject treated with the study drug. Study personnel at each site will enter data from source documents corresponding to a subject's visit into the protocol-specific VA Research Electronic Data Capture (REDCap) when the information corresponding to that visit is available. Subjects will not be identified by name in the study database or on any study documents to be collected by the Sponsor (or designee), but will be identified by a study ID and acronym.

The Investigator is responsible for all information collected on subjects enrolled in this study. All data collected during the course of this study must be reviewed and verified for completeness and accuracy by the Investigator.

15.2 Data Management Procedures

The data will be entered into a validated database. The Data Management group will be responsible for data processing, in accordance with procedural documentation. Database lock will occur once quality assurance procedures have been completed.

All procedures for the handling and analysis of data will be conducted using good computing practices meeting FDA guidelines for the handling and analysis of data for clinical trials.

15.3 Data Quality Control and Reporting

After data have been entered into the study database, a system of computerized data validation checks will be implemented and applied to the database on a regular basis. The study database will be updated in accordance with the resolved queries. All changes to the study database will be documented.

15.4 Archival of Data

The database is safeguarded against unauthorized access by established security procedures; appropriate backup copies of the database and related software files will be maintained. Databases are backed up by the database administrator in conjunction with any updates or changes to the database.

At critical junctures of the protocol (e.g., production of interim reports and final reports), data for analysis is locked and cleaned per established procedures.

15.5 Availability and Retention of Investigational Records

The Investigator must make study data accessible to the monitor, other authorized representatives of the Sponsor (Department of Veterans Affairs or designee), IRB/IEC, and Regulatory Agency (e.g., FDA) inspectors upon request. A file for each subject must be maintained that includes the signed Informed Consent, HIPAA Authorization and Assent Form and copies of all source documentation related to that subject. The Investigator must ensure the reliability and availability of source documents from which the information on the CRF was derived.

All study documents (patient files, signed informed consent forms, copies of CRFs, Study File Notebook, etc.) must be kept secured for a period of two years following marketing of the investigational product or for two years after centers have been notified that the IND has been discontinued. There may be other circumstances for which the Sponsor is required to maintain study records and, therefore, the Sponsor should be contacted prior to removing study records for any reason.

15.6 Monitoring

Monitoring visits will be conducted by representatives of the Sponsor according to the U.S. CFR Title 21 Parts 50, 56, and 312 and ICH Guidelines for GCP (E6). By signing this protocol, the Investigator grants permission to the Sponsor (or designee), and appropriate regulatory authorities to conduct on-site monitoring and/or auditing of all appropriate study documentation.

15.7 Subject Confidentiality

Informed consent will be obtained by the study coordinator, PI, or a trained other investigator. The process will take place either in the SFVAMC CTSI CRC; the UCSF Radiology Human Imaging Core Services (China Basin campus); the SFVAMC Endocrinology/Metabolism Clinic;

or in the Principal Investigator's office. In a private interview room, the study team member will explain the informed consent form. The study team member will talk through the form and its contents, allowing the potential participant the opportunity to answer questions and checking for understanding. If the potential participant wishes to enroll in the study, he will sign the informed consent form. Only after the form is signed will any study activities commence.

In order to maintain subject confidentiality, only a study ID and acrostic will identify all study subjects on CRFs and other documentation submitted to the Sponsor. Additional subject confidentiality issues (if applicable) are covered in the Clinical Study Agreement.

All data will be kept secure and confidential in locked cabinets in locked rooms on locked wards, and in password-protected electronic files. The data will be coded, so that participant identifiers do not exist in our database. Stored specimens will be de-identified, labeled with codes instead of personal information. Publications will not identify participants in any way.

16 ADMINISTRATIVE, ETHICAL, REGULATORY CONSIDERATIONS

The study will be conducted according to the Declaration of Helsinki, Protection of Human Volunteers (21 CFR 50), Institutional Review Boards (21 CFR 56), and Obligations of Clinical Investigators (21 CFR 312).

To maintain confidentiality, all laboratory specimens, evaluation forms, reports and other records will be identified by a study ID number and acrostic only. All study records will be kept in a locked file cabinet and code sheets linking a patient's name to a patient identification number will be stored separately in another locked file cabinet. Clinical information will not be released without written permission of the subject, except as necessary for monitoring by the FDA. The Investigator must also comply with all applicable privacy regulations (e.g., Health Insurance Portability and Accountability Act of 1996, EU Data Protection Directive 95/46/EC).

16.1 Protocol Amendments

Protocol amendments cannot be implemented without prior written IRB/IEC approval except as necessary to eliminate immediate safety hazards to patients. A protocol amendment intended to eliminate an apparent immediate hazard to patients may be implemented immediately, provided the IRB is notified within five working days.

16.2 Institutional Review Boards and Independent Ethics Committees

The protocol and consent form will be reviewed and approved by the IRB/IEC prior to study initiation. Serious adverse experiences regardless of causality will be reported to the IRB/IEC in accordance with the standard operating procedures and policies of the IRB/IEC, and the Investigator will keep the IRB/IEC informed as to the progress of the study. The Investigator will obtain assurance of IRB/IEC compliance with regulations.

Any documents that the IRB/IEC may need to fulfill its responsibilities (such as protocol, protocol amendments, Investigator's Brochure, consent forms, information concerning patient recruitment, payment or compensation procedures, or other pertinent information) will be submitted to the IRB/IEC. The IRB/IECs written unconditional approval of the study protocol and the informed consent form will be in the possession of the Investigator before the study is initiated. The IRB/IECs unconditional approval statement will be transmitted by the Investigator to the Sponsor or designee prior to the shipment of study supplies to the site. This approval must refer to the study by exact protocol title and number and should identify the documents reviewed and the date of review.

Protocol and/or informed consent modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the patients or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted and subsequently approved should be obtained.

The IRB/IEC must be informed of revisions to other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study in accordance with the standard operating procedures and policies of the IRB; new information that may affect adversely the safety of the patients of the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

16.3 Informed Consent Form

Informed consent will be obtained in accordance with the Declaration of Helsinki, ICH GCP, US Code of Federal Regulations for Protection of Human Subjects (21 CFR 50.25[a,b], CFR 50.27, and CFR Part 56, Subpart A), the Health Insurance Portability and Accountability Act (HIPAA, if applicable), and local regulations.

The Investigator will prepare the informed consent form, assent and HIPAA authorization and provide the documents to the Sponsor (the Department of Veterans Affairs and the VA Research Office), for approval prior to submission to the IRB/IEC. The consent form generated by the Investigator must be acceptable to the Department of Veterans Affairs and the VA Research Office and be approved by the IRB/IEC. The written consent document will embody the elements of informed consent as described in the International Conference on Harmonisation and will also comply with local regulations. The Investigator will send an IRB/IEC-approved copy of the Informed Consent Form to the Sponsor (the Department of Veterans Affairs and the VA Research Office) for the study file.

A properly executed, written, informed consent will be obtained from each subject prior to entering the subject into the trial. Information should be given in both oral and written form and subjects must be given ample opportunity to inquire about details of the study. If appropriate and required by the local IRB/IEC, assent from the subject will also be obtained. If a subject is unable to sign the informed consent form (ICF) and the HIPAA authorization, a legal representative may sign for the subject. A copy of the signed consent form (and assent) will be given to the subject and the original will be maintained with the subject's records.

16.4 Publications

The preparation and submittal for publication of manuscripts containing the study results shall be in accordance with a process determined by mutual written agreement among the study Sponsor and participating institutions. The publication or presentation of any study results shall comply with all applicable privacy laws, including, but not limited to, the Health Insurance Portability and Accountability Act of 1996.

16.5 Investigator Responsibilities

By signing the Agreement of Investigator form, the Investigator agrees to:

1. Conduct the study in accordance with the protocol and only make changes after notifying the Sponsor (the Department of Veterans Affairs and the VA Research Office), except when to protect the safety, rights or welfare of subjects.
2. Personally conduct or supervise the study (or clinical trial).

- 3.Ensure that the requirements relating to obtaining informed consent and IRB review and approval meet federal guidelines, as stated in § 21 CFR, parts 50 and 56.
- 4.Report to the Sponsor (the Department of Veterans Affairs and the VA Research Office), any AEs that occur in the course of the study, in accordance with §21 CFR 312.64.
- 5.Ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations in meeting the above commitments.
- 6.Maintain adequate and accurate records in accordance with §21 CFR 312.62 and to make those records available for inspection with the Sponsor (the Department of Veterans Affairs and the VA Research Office) or the UCSF IRB.
- 7.Ensure that an IRB that complies with the requirements of §21 CFR part 56 will be responsible for initial and continuing review and approval of the clinical study.
- 8.Promptly report to the IRB and the Sponsor (the Department of Veterans Affairs and the VA Research Office) all changes in the research activity and all unanticipated problems involving risks to subjects or others (to include amendments and IND safety reports).
- 9.Seek IRB approval and VA Research Service approval before any changes are made in the research study, except when necessary to eliminate hazards to the patients/subjects.
- 10.Comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements listed in § 21 CFR part 312.
- 11.Comply with all the rules and regulations of the Department of Veterans Affairs regarding the conduct of a Department of Veterans Affairs-sponsored clinical trial which includes preparing for, meeting with by teleconference, and addressing all the concerns and requests of the VA CSR&D Data Safety Monitoring Committee (DMC).

APPENDIX 1. SCHEDULE OF EVENTS

Evaluations	Screen Visit 1	Screen Visit 2*	Randomization	Week 1 (lab, phone, opt in-person)	Week 4 (~Month 1)	Week 8 (~Month 2)	Week 12 (~Month 3)	Week 20 (~Month 5)	Week 24 (~Month 6)	Week 36 (~Month 9)	Week 48 (~Month 11)
History, exam, FFQ		•									•
Concomitant meds		•	•	•	•	•	•	•	•	•	•
Vital signs		•	•		•	•	•	•	•	•	•
Screening labs		•									
DXA/TBS	•										•
24-hour urine Ca, Cr, Na		•	•		•	•	•		•	•	•
TPTD pen teaching		•	•								
PD study			•								
Extra blood collection			•	•	•	•	•	•	•	•	•
Collect PBMCs			•		•	•	•		•	•	•
Assess AEs		•	•	•	•	•	•	•	•	•	•
Ca and vitamin D intake check		•	•	•	•	•	•	•	•	•	•
Study drug dispensing		Ca/D only	•		•	•	•	•	•	•	

APPENDIX #2:**Taken from STUDY OPERATIONS MANUAL****Chapter 11. Hypercalcemia, Hypocalcemia, and Hypercalciuria Management****11.1. Hypercalcemia Algorithm (Figure 11-1)**

The Principal Investigator must be notified immediately upon receipt or notification of blood test results in a research subject that indicate hypercalcemia. If the Principal Investigator is away from the clinic, then his/her back-up physician must be notified. The **Hypercalcemia Algorithms** must be followed by the research study team. Sound clinical judgement will be exercised in the execution of this algorithm by the Principal Investigator and study physicians.

Hypercalcemia (lab values) will be recorded both on the **Hypercalcemia Case Report Form** and the **Adverse Event Form**.

Definition: albumin-corrected total serum calcium values ≥ 10.5 mg/dL are defined as hypercalcemia. The following formula is used to calculate the albumin-corrected total serum calcium level using measured serum calcium (mg/dL) and serum albumin (G/dL) levels.

Serum total calcium (mg/dL) + $0.8 \times [4.0 - \text{measured serum albumin (G/dL)}]$ = albumin-corrected total serum calcium (mg/dL)

11.1.1. HYPERCALCEMIA WITH AN ALBUMIN-CORRECTED TOTAL SERUM CALCIUM VALUE BETWEEN 10.5 – 11.2 mg/dL [ALGORITHM A]

If a participant's test result indicates that the albumin-corrected total serum calcium concentration is between 10.5 - 11.2 mg/dL (blood test 1), **Algorithm A** should be followed. The participant should be contacted and brought into the clinic for a re-test within one week. The research study clinician or coordinator will explain to the subject that it is necessary to repeat one blood test to check the level of calcium in his blood.

11.1.2. Re-test (Blood Test 2)

If the re-test (blood test 2) results indicate:

Outcome 1: albumin-corrected total serum calcium concentration is < 10.5 mg/dL. The participant may continue in the study. This finding indicates that either the results of the earlier blood test were anomalous or that serum calcium levels have returned to normal. Either way, it is safe for the participant to continue in the study with no changes to the study medications or supplement regimens. Because the original blood test indicated hypercalcemia, however, adverse event forms must be filled out at this point. Both the **Hypercalcemia Case Report Form** and the **Adverse Event Form** will be completed and maintained on file with our study documents and reported on to the VA Clinical Services Research and Development (CSR&D) Data Monitoring Committee (DMC) and the University of California (UCSF) Institutional Review Board (IRB), according to their individual reporting requirements and on their regular reporting schedules.

Outcome 2: albumin-corrected serum calcium concentration is ≥ 10.5 mg/dL. An action is required. The participant should discontinue calcium and vitamin D supplements and return to the clinic to be re-tested within 2 weeks. Because calcium supplements are being stopped, the participant should be counseled about continuing to get sufficient calcium from his diet. Other study medications will be continued including teriparatide injections and cinacalcet or placebo tablets.

11.1.3. Re-test (Blood Test 3)

If the re-test results (blood test 3) indicate:

Outcome 1: albumin-corrected total serum calcium is <10.5 mg/dL. The participant may continue in the study but should no longer take the calcium supplements. Vitamin D supplements should be reinstated. Adverse event forms must be filled out at this point. Both the **Hypercalcemia Case Report Form** and the **Adverse Event Form** will be completed and maintained on file with our study documents and reported on to the VA CSR&D DMC and the UCSF IRB, according to their individual reporting requirements and on their regular reporting schedules.

Outcome 2: albumin-corrected total serum calcium is ≥ 10.5 mg/dL. The participant should reduce the frequency of PTH injections to every other day, reduce the frequency of cinacalcet or placebo tablets to every other day, and return to the clinic to be re-tested in 2 weeks. The participant should not be taking the calcium or vitamin D supplements.

11.1.4. Re-test (Blood Test 4)

If the re-test results (blood test 4) indicate:

Outcome 1: albumin-corrected total serum calcium is <10.5 mg/dL. This is a normal finding, and this subject's assessment and changes in management are now complete. The participant may continue in the study with the frequency of PTH injections and the frequency of taking cinacalcet or placebo tablets both being every other day, but the participant should not take the calcium supplements. Vitamin D supplements should be re-instated. Adverse event forms must be filled out at this point. Both the **Hypercalcemia Case Report Form** and the **Adverse Event Form** will be completed and maintained on file with our study documents and reported on to the VA CSR&D DMC and the UCSF IRB, according to their individual reporting requirements and on their regular reporting schedules.

Outcome 2: albumin-corrected total serum calcium is ≥ 10.5 mg/dL. The participant must be withdrawn from PTH injections and from cinacalcet or placebo tablets for safety reasons. He should discontinue PTH injections and cinacalcet or placebo tablets and return to the clinic to be retested in 2 weeks. The participant should also not be taking the calcium or vitamin D supplements.

11.1.5. Re-test (Blood Test 5)

If the re-test results (blood test 5) indicate:

Outcome 1: albumin-corrected total serum calcium level has returned to normal (<10.5 mg/dL). No further action is required. The participant should not resume PTH injections or taking cinacalcet or placebo tablets during the remainder of the study. He may resume calcium and vitamin D supplements and be followed up in the study per the protocol. Adverse event forms must be filled out at this point. Both the **Hypercalcemia Case Report Form** and the **Adverse Event Form** will be completed and maintained on file with our study documents and reported on to the VA CSR&D DMC and the UCSF IRB, according to their individual reporting requirements and on their regular reporting schedules.

Outcome 2: albumin-corrected total serum calcium level has not returned to normal (≥ 10.5 mg/dL). The subject has already been discontinued from PTH injections and cinacalcet or placebo tablets, and he must remain off these study medications during the remainder of the study. He should be referred to his physician for appropriate diagnosis and management. He should not resume calcium and vitamin D supplements until his serum calcium levels have returned to normal. His assessment for hypercalcemia in the trial is now complete. Adverse event forms must be filled out at this point. Both the **Hypercalcemia Case Report Form** and the **Adverse Event Form** will be completed and maintained on file with our study documents and reported on to the VA CSR&D DMC and the UCSF IRB, according to their individual reporting requirements and on their regular reporting schedules.

11.1.6. HYPERCALCEMIA WITH AN ALBUMIN-CORRECTED TOTAL SERUM CALCIUM VALUE > 11.2 mg/dL [ALGORITHM B]

If the re-test results indicate albumin-corrected total serum calcium is >11.2 mg/dL, **Algorithm B** should be followed. The participant should be contacted immediately and brought into the clinic for a re-test as soon as possible and within 1 week. The clinician or study coordinator should explain that it is necessary to repeat one of the blood tests in order to check the level of calcium in his blood. The clinician or study coordinator should be reassuring, while still stressing the importance of returning for this test as soon as he can.

11.1.6.1. Re-test (Blood Test 2)

If the re-test results (blood test 2) indicate:

Outcome 1: albumin-corrected total serum calcium is <10.5 mg/dL. The participant may continue in the study. This finding indicates that either the results of the earlier blood test were anomalous or that serum calcium levels have returned to normal. Either way, it is safe for the participant to continue in the study with no changes to study medication or supplement regimens. Because the original blood test indicated hypercalcemia, however, adverse event forms must be filled out at this point. Both the **Hypercalcemia Case Report Form** and the **Adverse Event Form** will be completed and maintained on file with our study documents and reported on to the VA CSR&D DMC and the UCSF IRB, according to their individual reporting requirements and on their regular reporting schedules.

Outcome 2: albumin-corrected total serum calcium is between 10.5-11.2 mg/dL. **Algorithm A** (detailed above) should be followed. The participant should discontinue calcium and vitamin D supplements and return to the clinic to be re-tested in 2 weeks. Because calcium supplements are being stopped, the participant should be counseled about getting sufficient dietary calcium. Continue with **Algorithm A** (instructions as above).

Outcome 3: albumin-corrected total serum calcium is >11.2 mg/dL. The participant should reduce the PTH injection frequency to every other day, reduce the cinacalcet or placebo tablets to every other day, discontinue calcium and vitamin D supplements, and return to the clinic to be re-tested in 2 weeks. Because calcium supplements are being stopped, the participant should be counseled about getting sufficient dietary calcium.

11.1.6.2. Re-test (Blood Test 3)

If the re-test results (blood test 3) indicate:

Outcome 1: albumin-corrected total serum calcium is <10.5 mg/dL. The participant may continue in the study taking PTH injections every other day and taking cinacalcet or placebo tablets every other day. Vitamin D supplements should be re-instated, but the participant should discontinue calcium. Because the original blood test indicated hypercalcemia, however, adverse event forms must be filled out at this point. Both the **Hypercalcemia Case Report Form** and the **Adverse Event Form** will be completed and maintained on file with our study documents and reported on to the VA CSR&D DMC and the UCSF IRB, according to their individual reporting requirements and on their regular reporting schedules.

Outcome 2: albumin-corrected total serum calcium is ≥ 10.5 mg/dL. The participant should discontinue PTH injections and cinacalcet or placebo tablets and return to the clinic to be re-tested in 2 weeks. The participant should not take calcium or vitamin D supplements.

11.1.6.3. Re-test (Blood Test 4)

If the re-test results (blood test 4) indicate:

Outcome 1: albumin-corrected total serum calcium level has returned to normal (<10.5 mg/dL). No further action is required as regards study medications. The participant should not resume PTH injections or cinacalcet or placebo tablets during the remainder of the study. He may resume calcium and vitamin D supplements according to the study protocol. Because the original blood test indicated hypercalcemia, however, adverse event forms must be filled out at this point. Both the **Hypercalcemia Case Report Form** and the **Adverse Event Form** will be completed and maintained on file with our study documents and reported on to the VA CSR&D DMC and the UCSF IRB, according to their individual reporting requirements and on their regular reporting schedules.

Outcome 2: albumin-corrected total serum calcium level has not returned to normal (≥ 10.5 mg/dL). The participant should be referred to his physician for appropriate management and treatment. The participant should not resume PTH injections or cinacalcet or placebo tablets during the study. He should not resume calcium and vitamin D supplements until his serum calcium levels have returned to normal. Because the original blood test indicated hypercalcemia, however, adverse event forms must be filled out at this point. Both the **Hypercalcemia Case Report Form** and the **Adverse Event Form** will be completed and maintained on file with our study documents and reported on to the VA Clinical Services Research and Development (CSR&D) Data Monitoring Committee (DMC) and the University of California (UCSF) Institutional Review Board (IRB), according to their individual reporting requirements and on their regular reporting schedules.

11.2. Filling out the Hypercalcemia Case Report Form

The **Hypercalcemia Case Report Form** is updated as results of blood tests come into the clinic. The form should not be signed off and stored until it is complete. The form is considered complete when no further action is required for the participant. When the form is complete, an **Adverse Event Form** should also be filled out.

11.3. Hypocalcemia Algorithm (Figure 11-2)

The Principal Investigator must be notified immediately upon receipt or notification of blood test results in a research subject that indicate hypocalcemia. If the Principal Investigator is away from the clinic, then his/her back-up physician must be notified. The **Hypocalcemia Algorithms** must be followed by the research study team. Sound clinical judgement will be exercised in the execution of this algorithm by the Principal Investigator and study physicians.

Hypocalcemia (lab values) will be recorded both on the **Hypocalcemia Case Report Form** and the **Adverse Event Form**.

Definition: albumin-corrected total serum calcium values < 8.5 mg/dL are defined as hypocalcemia. The following formula is used to calculate the albumin-corrected total serum calcium level using measuring serum calcium (mg/dL) and serum albumin (G/dL) levels.

Serum total calcium (mg/dL) + 0.8 X [4.0-measured serum albumin (G/dL)] = albumin-corrected total serum calcium (mg/dL)

Albumin-corrected serum calcium $\geq$ 8.5 mg/dL is not considered hypocalcemia, and no action needs to be taken.

11.3.1. HYPOCALCEMIA WITH A SERUM ALBUMIN-CORRECTED TOTAL CALCIUM BETWEEN 8.0 – 8.4 mg/dL [ALGORITHM C]

If a participant's test result indicates that the albumin-corrected total serum calcium level is between 8.0 - 8.4 mg/dL, **Algorithm C** should be followed. The participant should be contacted and brought into the clinic for a re-test within one week. The clinician or clinical coordinator will explain that it is necessary to repeat one blood test to check the level of calcium in his blood.

11.3.1.1. Re-test (Blood Test 2)

If the re-test (blood test 2) results indicate:

Outcome 1: albumin-corrected total serum calcium is $\geq$ 8.5 mg/dL. The participant may continue in the study. This finding indicates that either the results of the earlier blood test were anomalous or that serum calcium levels have returned to normal. Either way, it is safe for the participant to continue in the study with no changes to the study medication or supplement regimens. Because the original blood test indicated hypocalcemia, however, adverse event forms must be filled out at this point. Both the **Hypocalcemia Case Report Form** and the

Adverse Event Form will be completed and maintained on file with our study documents and reported on to the VA CSR&D DMC and the UCSF IRB, according to their individual reporting requirements and on their regular reporting schedules.

Outcome 2: albumin-corrected total serum calcium is < 8.5 mg/dL. Action is required. The participant should increase total daily calcium supplements by 400 mg (up to a maximum daily intake of 2000 mg/day) and increase vitamin D supplements by 2000 IU daily if the most recent serum 25OH vitamin D level was 20 to 30 ng/ml. Ergocalciferol (50,000 IU three times weekly for 3 weeks) may be added, if the most recent serum 25OH vitamin D levels was < 20 ng/ml with a goal of reaching a 25OH vitamin D level of $\geq$ 30 ng/ml. The participant will be asked to return to the clinic to be re-tested in 2 weeks. The participant should also be counseled about getting sufficient calcium from his diet.

11.3.1.2. Re-test (Blood Test 3)

If the re-test results (blood test 3) indicate:

Outcome 1: albumin-corrected total serum calcium is $\geq$ 8.5 mg/dL. The participant may continue in the study and should continue with calcium and vitamin D supplements and study medications per protocol. Because the original blood test indicated hypocalcemia, however, adverse event forms must be filled out at this point. Both the **Hypocalcemia Case Report Form** and the **Adverse Event Form** will be completed and maintained on file with our study documents and reported on to the VA CSR&D DMC and the UCSF IRB, according to their individual reporting requirements and on their regular reporting schedules.

Outcome 2: albumin-corrected total serum calcium is < 8.5 mg/dL. The participant will be asked to change the frequency of cinacalcet or placebo tablets to every other day, to continue the teriparatide injections daily, and to return to the clinic to be re-tested in 2 weeks. The participant should continue taking the calcium and vitamin D supplements. Serum 25OH vitamin D levels will be monitored with this lab test.

11.3.1.3. Re-test (Blood Test 4)

If the re-test results (blood test 4) indicate:

Outcome 1: albumin-corrected total serum calcium is $\geq$ 8.5 mg/dL. This is a normal serum calcium level, and testing is now complete. The participant may continue in the study at the same dose of cinacalcet every other day, but should continue the increased dose of calcium supplements. Vitamin D supplements should be continued. Because the original blood test indicated hypocalcemia, however, adverse event forms must be filled out at this point. Both the **Hypocalcemia Case Report Form** and the **Adverse Event Form** will be completed and maintained on file with our study documents and reported on to the VA CSR&D DMC and the UCSF IRB, according to their individual reporting requirements and on their regular reporting schedules.

Outcome 2: albumin-corrected total serum calcium is < 8.5 mg/dL. The participant must be withdrawn from cinacalcet or placebo tablets. He should continue to take teriparatide injections daily and calcium and vitamin D supplements and return to the clinic to be retested in 2 weeks.

11.3.1.4. Re-test (Blood Test 5)

If the re-test results (blood test 5) indicate:

Outcome 1: albumin-corrected total serum calcium is ≥ 8.5 mg/dL. This is normal, and no further action is required. The participant should continue to take teriparatide injections daily and calcium and vitamin D supplements. Because the original blood test indicated hypocalcemia, however, adverse event forms must be filled out at this point. Both the **Hypocalcemia Case Report Form** and the **Adverse Event Form** will be completed and maintained on file with our study documents and reported on to the VA VA CSR&D DMC and the UCSF IRB, according to their individual reporting requirements and on their regular reporting schedules.

Outcome 2: albumin-corrected total serum calcium level is < 8.5 mg/dL. The participant should be referred to his physician for appropriate management and treatment. The participant should not resume cinacalcet or placebo but continue calcium and vitamin D supplements and teriparatide injections and be followed up per protocol in the study. The subject should be given an increased total daily dose of calcium supplements (up to a maximum daily intake of 2500 mg/day) until his serum calcium levels have returned to normal. His 25OH vitamin D levels should be checked. Vitamin D supplements can be added (in 1000 IU increments daily) if the 25OH vitamin D level is 20-30 ng/ml, or ergocalciferol 50,000 IU three times weekly can be given for 3 weeks if the 25OH vitamin D level is < 20 ng/ml to reach 25OH vitamin D level of ≥ 30 ng/ml or higher. Because the original blood test indicated hypocalcemia, however, adverse event forms must be filled out at this point. Both the **Hypocalcemia Case Report Form** and the **Adverse Event Form** will be completed and maintained on file with our study documents and reported on to the VA CSR&D DMC and the UCSF IRB, according to their individual reporting requirements and on their regular reporting schedules.

11.3.2. HYPOCALCEMIA WITH A SERUM ALBUMIN-CORRECTED TOTAL CALCIUM LESS THAN 8.0 mg/dL [ALGORITHMS D and E]

11.3.2.1. ALBUMIN-CORRECTED TOTAL SERUM CALCIUM 7.5-7.9 mg/dL [ALGORITHM D]

If a participant's test or re-test results indicate albumin-corrected total serum calcium is between 7.5 and 7.9 mg/dL, **Algorithm D** should be followed. The participant should be contacted immediately and brought into the clinic to examine for symptoms of hypocalcemia and for a re-test as soon as possible. The clinician or clinical coordinator should explain that it is necessary to repeat one of the blood tests in order to check the level of calcium in his blood. The examiner should be reassuring while still stressing the importance of returning for this test as soon as he can.

11.3.2.1.1. Re-test (Blood Test 2)

If the re-test results (blood test 2) indicate:

Outcome 1: albumin-corrected total serum calcium is ≥ 8.5 mg/dL. The participant may continue in the study. This finding indicates that either the results of the earlier blood test were anomalous or that serum calcium levels have returned to normal. Either way, it is safe for the participant to continue in the study with no changes to study medication or supplement

regimens. Because the original blood test indicated hypocalcemia, however, adverse event forms must be filled out at this point. Both the **Hypocalcemia Case Report Form** and the **Adverse Event Form** will be completed and maintained on file with our study documents and reported on to the VA CSR&D DMC and the UCSF IRB, according to their individual reporting requirements and on their regular reporting schedules

Outcome 2: albumin-corrected total serum calcium is between 8.0 - 8.4 mg/dL. **Algorithm C** should be followed. Action is required. The participant should increase total daily calcium supplements by 400 mg (up to a maximum daily intake of 2000 mg/day) and increase vitamin D supplements by 2000 IU daily if the most recent serum 25OH vitamin D level was 20 to 30 ng/ml. Ergocalciferol (50,000 IU three times weekly for 3 weeks) may be added, if the most recent serum 25OH vitamin D levels was < 20 ng/ml with a goal of reaching a 25OH vitamin D level of ≥ 30 ng/ml. The participant will be asked to return to the clinic to be re-tested in 2 weeks. The participant should also be counseled about getting sufficient calcium from his diet.

Outcome 3: albumin-corrected total serum calcium is <8.0 mg/dL. The participant should change the frequency of taking cinacalcet or placebo tablets to every other day and continue daily teriparatide injections. He should increase total daily calcium supplements by 400 to 1000 mg (up to a maximum daily intake of 2000 mg/day) as well as vitamin D supplements by 2000 IU daily if 25OH vitamin D level is 20 to 30 ng/ml and with the addition of ergocalciferol 50,000 IU three times weekly for 3 weeks if 25OH vitamin D is < 20 ng/ml to reach 25OH vitamin D level ≥ 30 ng/ml. Calcitriol 0.25 mcg once or twice daily may be added, and the participant will be asked to return to the clinic to be re-tested in 1 week. Participant should also be counseled about getting sufficient dietary calcium.

11.3.2.1.2. Re-test (Blood Test 3)

If the re-test results (blood test 3) indicate:

Outcome 1: albumin-corrected total serum calcium is ≥ 8.5 mg/dL. The participant may continue in the study on cinacalcet or placebo every other daily and daily teriparatide injections. Vitamin D and calcium supplements should be continued at the established doses. 25 OH vitamin D level will be checked. Because the original blood test indicated hypocalcemia, however, adverse event forms must be filled out at this point. Both the **Hypocalcemia Case Report Form** and the **Adverse Event Form** will be completed and maintained on file with our study documents and reported on to the VA CSR&D DMC and the UCSF IRB, according to their individual reporting requirements and on their regular reporting schedules.

Outcome 2: albumin-corrected total serum calcium is between 7.5-8.4 mg/dL. The participant should discontinue cinacalcet or placebo tablets and return to the clinic to be re-tested in 1 week. 25 OH vitamin D level will be checked. The participant should increase total daily calcium supplements by 400 mg (up to a maximum daily intake of 2500 mg/day) as well as vitamin D supplements if the serum 25 OH vitamin D level is < 30 ng/ml. Vitamin D (2000 IU daily) may be added if 25OH vitamin D is 20-30 ng/ml, or ergocalciferol (50,000 IU three times weekly for 3 weeks) may be added if the 25OH vitamin D level is < 20 ng/ml in order to reach 25OH vitamin D level of ≥ 30 ng/ml. Calcitriol 0.25 mcg once daily may be added if serum calcium is less than 8.0 mg/dL and or symptoms of hypocalcemia are present at the investigator's discretion.

Outcome 3: albumin-corrected total serum calcium is < 7.5 mg/dL. The participant should be referred to his physician for appropriate IV treatment and intensified oral supplementation with calcium and calcitriol. The participant should not resume cinacalcet or placebo tablets during the study but should be followed up per protocol. He should return to the clinic in one week for testing. He should continue daily teriparatide injections. He should increase total daily calcium supplements by 400 mg (up to a maximum daily intake of 2500 mg/day) until his serum calcium levels have returned to normal. He should be told to increase vitamin D supplements by 2000 IU daily if 25OH vitamin D levels are 20-30 ng/ml and consider adding ergocalciferol 50,000 IU three times weekly for 3 weeks if the 25OH vitamin D level is < 20 ng/ml to reach 25OH vitamin D level of ≥ 30 ng/ml. Calcitriol 0.25 mcg once or twice daily may be added at the investigator's discretion.

11.3.2.1.3. Re-test (Blood Test 4)

If the re-test results (blood test 4) indicate:

Outcome 1: albumin-corrected total serum calcium levels are normal at ≥ 8.5 mg/dL. No further action is required. The participant should not resume cinacalcet or placebo tablets during the study. He may continue calcium and vitamin D supplements and daily teriparatide injections. Calcium and vitamin D supplements can be slowly titrated to reach levels in the study protocol as tolerated, while maintaining a normal serum calcium level. Because the original blood test indicated hypocalcemia, however, adverse event forms must be filled out at this point. Both the **Hypocalcemia Case Report Form** and the **Adverse Event Form** will be completed and maintained on file with our study documents and reported on to the VA CSR&D DMC and the UCSF IRB, according to their individual reporting requirements and on their regular reporting schedules.

Outcome 2: albumin-corrected total serum calcium levels have not returned to normal (remain < 8.5 mg/dL). The participant should be referred to his physician for appropriate management. The participant should not resume cinacalcet or placebo tablets during the study. He should continue daily teriparatide injections. He should increase total daily calcium supplements by 400 mg (up to a maximum daily intake of 2500 mg/day) until his serum calcium levels have returned to normal as well as increase vitamin D supplements by 2000 IU daily if 25OH vitamin D levels are 20-30 ng/ml and with the addition of ergocalciferol (50,000 IU three times weekly for 3 weeks) if 25OH vitamin D levels are < 20 ng/ml to reach 25OH vitamin D ≥ 30 ng/ml. The study physician may add calcitriol 0.25 mcg once daily if the serum calcium level is < 8.0 mg/dL or twice daily if calcium is < 7.5 mg/dL. The participant should be seen in the clinic and re-tested in 1 week. **Algorithm C** should be followed.

11.3.2.2. ALBUMIN-CORRECTED TOTAL SERUM CALCIUM < 7.5 mg/dL [ALGORITHM E]

If a participant's test or re-test results indicate albumin-corrected total serum calcium is < 7.5 mg/dL, **Algorithm E** should be followed. The participant should be contacted immediately and brought into the clinic to examine for symptoms of hypocalcemia and for a re-test as soon as possible. The clinician or clinical coordinator should explain that it is necessary to repeat one of the blood tests in order to check the level of calcium in his blood. The examiner should be reassuring while still stressing the importance of returning for this test as soon as he can.

11.3.2.2.1. Re-test (Blood Test 2)

If the re-test results (blood test 2) indicate:

Outcome 1: albumin-corrected total serum calcium is ≥ 8.5 mg/dL. The participant may continue in the study. This finding indicates that either the results of the earlier blood test were anomalous or that serum calcium levels have returned to normal. Either way, it is safe for the participant to continue in the study with no changes to study medication or supplement regimens. Because the original blood test indicated hypocalcemia, however, adverse event forms must be filled out at this point. Both the **Hypocalcemia Case Report Form** and the **Adverse Event Form** will be completed and maintained on file with our study documents and reported on to the VA CSR&D DMC and the UCSF IRB, according to their individual reporting requirements and on their regular reporting schedules.

Outcome 2: albumin-corrected total serum calcium is between 8.0 – 8.4 mg/dL. **Algorithm C** should be followed.

Outcome 3: albumin-corrected total serum calcium is between 7.5-7.9 mg/dL. The participant should change the frequency of cinacalcet or placebo tablets to every other day and continue daily teriparatide injections. He should increase total daily calcium supplements by 400 mg (up to a maximum daily intake of 2500 mg/day) as well as vitamin D supplements by 2000 IU daily if 25OH vitamin D levels were 20-30 ng/ml and add ergocalciferol (50,000 IU three times weekly for 3 weeks) if 25OH vitamin D levels were < 20 ng/ml to reach 25OH vitamin D level of ≥ 30 ng/ml, and add calcitriol 0.25 mcg once daily. Return to the clinic to be re-tested in 1 week. The participant should also be counseled about getting sufficient dietary calcium. Continue with **Algorithm D**.

Outcome 4: albumin-corrected total serum calcium is < 7.5 mg/dL. The participant should discontinue cinacalcet or placebo tablets, continue daily teriparatide injections, and increase total daily calcium supplements by 400 mg (up to a maximum daily intake of 2500 mg/day) as well as vitamin D supplements by 2000 IU daily if 25OH vitamin D levels were 20-30 ng/ml and add ergocalciferol (50,000 IU three times weekly for 3 weeks) if 25OH vitamin D < 20 ng/ml to reach 25OH vitamin D ≥ 30 ng/ml, and add calcitriol 0.25 mcg twice daily. The participant should return to the clinic to be re-tested in 1 week. Participant should also be counseled about getting sufficient dietary calcium.

11.3.2.2.2. Re-test (Blood Test 3)

If the re-test results (blood test 3) indicate:

Outcome 1: albumin-corrected total serum calcium is ≥ 8.5 mg/dL. The participant may continue in the study per protocol on teriparatide injections. Cinacalcet or placebo tablets can be resumed every other day along with daily teriparatide injections. Vitamin D and calcium supplements should be continued. Because the original blood test indicated hypocalcemia, however, adverse event forms must be filled out at this point. Both the **Hypocalcemia Case Report Form** and the **Adverse Event Form** will be completed and maintained on file with our study documents and reported on to the VA CSR&D DMC and the UCSF IRB, according to their individual reporting requirements and on their regular reporting schedules.

Outcome 2: albumin-corrected total serum calcium is between 8.0-8.4 mg/dL. The participant should discontinue cinacalcet or placebo tablets, continue daily teriparatide injections, and

return to the clinic to be re-tested in 2 weeks. The participant should increase total daily calcium supplements by 400 mg (up to a maximum daily intake of 2500 mg/day) as well as vitamin D supplements by 2000 IU daily if 25OH vitamin D levels were 20-30 ng/ml and with the addition of ergocalciferol (50,000 IU three times weekly for 3 weeks) if 25OH vitamin D levels were < 20 ng/ml to reach 25OH vitamin D levels of ≥ 30 ng/ml, and add calcitriol 0.25 mcg once daily if symptoms are present.

Outcome 3: albumin-corrected total serum calcium is < 8.0 mg/dL. The participant should be referred to his physician for appropriate IV treatment. The participant should discontinue cinacalcet or placebo tablets, continue daily teriparatide injections, and return to the clinic to be re-tested in 1 week. The participant should not resume cinacalcet or placebo tablets during the study. He should increase total daily calcium supplements by 400 mg (up to a maximum daily intake of 2500 mg/day) until his serum calcium levels have returned to normal and increase vitamin D supplements by 2000 IU daily if 25OH vitamin D levels were 20-30 ng/ml and add ergocalciferol (50,000 IU three times weekly for 3 weeks) if 25OH vitamin D level was < 20 ng/ml to reach 25OH vitamin D levels ≥ 30 ng/ml, and add calcitriol 0.25 mcg once or twice daily if symptoms are present.

11.3.2.2.3. Re-test (Blood Test 4)

If the re-test results (blood test 4) indicate:

Outcome 1: albumin-corrected total serum calcium levels returned to normal (≥ 8.5 mg/dL). No further action is required. The participant should not resume cinacalcet or placebo tablets. He may continue calcium and vitamin D supplements and teriparatide injections and be followed up per the protocol. Because the original blood test indicated hypocalcemia, however, adverse event forms must be filled out at this point. Both the **Hypocalcemia Case Report Form** and the **Adverse Event Form** will be completed and maintained on file with our study documents and reported on to the VA CSR&D DMC and the UCSF IRB, according to their individual reporting requirements and on their regular reporting schedules.

Outcome 2: albumin-corrected total serum calcium levels have not returned to normal (<8.5 mg/dL). The research participant should be referred to his physician for appropriate ongoing diagnosis and treatment. The participant should not resume cinacalcet or placebo tablets during the study. He can continue daily teriparatide injections. He should increase total daily calcium supplements by 400 mg (up to a maximum daily intake of 2500 mg/day) until his serum calcium levels have returned to normal as well as increase vitamin D supplements until his 25 OH vitamin D level has returned to ≥ 30 ng/ml. Because the original blood test indicated hypocalcemia, however, adverse event forms must be filled out at this point. Both the **Hypocalcemia Case Report Form** and the **Adverse Event Form** will be completed and maintained on file with our study documents and reported on to the VA CSR&D DMC and the UCSF IRB, according to their individual reporting requirements and on their regular reporting schedules.

11.4. Use of Calcitriol in the Hypocalcemia Algorithm

In all of the above clinical situations of hypocalcemia in which calcitriol is used in study patients, this medication will be tapered off gradually after normocalcemia is attained with careful monitoring of serum calcium levels expected to be over 1 to 4 weeks.

11.5. Filling out the Hypocalcemia Case Report Form

The **Hypocalcemia Case Report Form** is updated as results of blood tests come into the clinic. The form should not be signed off and stored until it is complete. The form is considered complete when no further action is required for the participant. When the form is complete, an **Adverse Event Form** should also be filled out.

HYPERCALCIURIA

11.6 Hypercalciuria Algorithm (Figure 11-3)

The Principal Investigator must be notified that 24 hour urine test results in a research subject indicate hypercalciuria. If the Principal Investigator is away from the clinic, then his/her back-up physician must be notified. The **Hypercalciuria Algorithms** must be followed by the research study team. Sound clinical judgement will be exercised in the execution of this algorithm by the Principal Investigator and study physicians.

Hypercalciuria (lab values) will be recorded both on the **Hypercalciuria Case Report Form** and the **Adverse Event Form**.

Definition: 24 hour urine calcium values >400 mg/dL are defined as hypercalciuria.

11.6.1. HYPERCALCIURIA WITH A URINE CALCIUM VALUE > 400 mg/24 hours

If a participant's test result indicates that the urine calcium level is > 400 mg/ 24 hours (urine test 1), then the following **Algorithm** should be followed. The participant should be contacted and brought into the clinic for a re-test within two weeks. The research study clinician or coordinator will explain to the subject that it is necessary to repeat one urine test to check the level of calcium in his urine.

11.6.2. Re-test (Urine Test 2)

If the re-test (urine test 2) results indicate:

Outcome 1: the urine calcium level is ≤ 400 mg/24 hours. The participant may continue in the study. This finding indicates that either the results of the earlier blood test were anomalous or that urine calcium levels have returned to normal. Either way, it is safe for the participant to continue in the study with no changes to the study medications or supplement regimens. Because the urine test indicated hypercalciuria, however, adverse event forms must be filled out at this point. Both the **Hypercalciuria Case Report Form** and the **Adverse Event Form** will be completed and maintained on file with our study documents and reported on to the VA Clinical Services Research and Development (CSR&D) Data Monitoring Committee (DMC) and the University of California (UCSF) Institutional Review Board (IRB), according to their individual reporting requirements and on their regular reporting schedules.

Outcome 2: the urine calcium level is >400 mg/24 hours. An action is required. The participant should decrease the amount of calcium supplements by ~50% with the study team guidance and return to the clinic to be re-tested within 2 weeks. The participant's dietary calcium intake should

be reviewed to assure it is not excessive. Other study medications will be continued including teriparatide injections and cinacalcet or placebo tablets.

11.6.3. Re-test (Urine Test 3)

If the re-test (urine test 3) results indicate:

Outcome 1: the urine calcium level is ≤ 400 mg/24 hours. The participant may continue in the study at the reduced level of calcium supplements. It is safe for the participant to continue in the study with no changes to the other study medications (teriparatide, cinacalcet or placebo, or vitamin D). Because the urine test indicated hypercalciuria, however, adverse event forms must be filled out at this point. Both the **Hypercalciuria Case Report Form** and the **Adverse Event Form** will be completed and maintained on file with our study documents and reported on to the VA Clinical Services Research and Development (CSR&D) Data Monitoring Committee (DMC) and the University of California (UCSF) Institutional Review Board (IRB), according to their individual reporting requirements and on their regular reporting schedules.

Outcome 2: the urine calcium level is >400 mg/24 hours. An action is required. The participant should discontinue calcium supplements with the study team guidance and return to the clinic to be re-tested within 2 weeks. The participant's dietary calcium intake should be reviewed to assure it is not excessive. Other study medications will be continued including teriparatide injections and cinacalcet or placebo tablets.

11.6.4. Re-test (Urine Test 4)

If the re-test (urine test 4) results indicate:

Outcome 1: the urine calcium level is ≤ 400 mg/24 hours. The participant may continue in the study off all calcium supplements. It is safe for the participant to continue in the study with no changes to the other study medications (teriparatide, cinacalcet or placebo, or vitamin D). Because the urine test indicated hypercalciuria, however, adverse event forms must be filled out at this point. Both the **Hypercalciuria Case Report Form** and the **Adverse Event Form** will be completed and maintained on file with our study documents and reported on to the VA Clinical Services Research and Development (CSR&D) Data Monitoring Committee (DMC) and the University of California (UCSF) Institutional Review Board (IRB), according to their individual reporting requirements and on their regular reporting schedules.

Outcome 2: the urine calcium level is >400 mg/24 hours. An action is required. The participant should continue to remain off calcium supplements with the study team guidance. Other study medications (teriparatide injections and cinacalcet or placebo tablets) should be reduced to every other day. The participant should return to the clinic to be re-tested within 2 weeks. The participant's dietary calcium intake should be reviewed to assure it is not excessive. Vitamin D supplements should be reviewed to assure they are not excessive and a 25 OH vitamin D level will be obtained. Vitamin D supplements are maintained.

11.6.5. Re-test (Urine Test 5)

If the re-test (urine test 5) results indicate:

Outcome 1: the urine calcium level is ≤ 400 mg/24 hours. The participant may continue in the study off all calcium supplements and taking study medications (teriparatide, cinacalcet or placebo) every other day. Because the urine test indicated hypercalciuria, however, adverse event forms must be filled out at this point. Both the **Hypercalciuria Case Report Form** and the **Adverse Event Form** will be completed and maintained on file with our study documents and reported on to the VA Clinical Services Research and Development (CSR&D) Data Monitoring Committee (DMC) and the University of California (UCSF) Institutional Review Board (IRB), according to their individual reporting requirements and on their regular reporting schedules.

Outcome 2: the urine calcium level is >400 mg/24 hours. The participant should continue to remain off calcium supplements with the study team guidance. Other study medications (teriparatide injections and cinacalcet or placebo tablets) should be discontinued. The participant should return to the clinic to be re-tested within 2 weeks. The participant's dietary calcium intake should be reviewed to assure it is not excessive. Vitamin D supplements should be discontinued and the participant should be referred to his physician for ongoing care. The subject can be continued in the study and perform the followup study procedures. Because the urine test indicated hypercalciuria, however, adverse event forms must be filled out at this point. Both the **Hypercalciuria Case Report Form** and the **Adverse Event Form** will be completed and maintained on file with our study documents and reported on to the VA Clinical Services Research and Development (CSR&D) Data Monitoring Committee (DMC) and the University of California (UCSF) Institutional Review Board (IRB), according to their individual reporting requirements and on their regular reporting schedules.

11.6.6. Filling out the Hypercalciuria Case Report Form

The **Hypercalciuria Case Report Form** is updated as results of urine tests come into the clinic. The form should not be signed off and stored until it is complete. The form is considered complete when no further action is required for the participant. When the form is complete, an **Adverse Event Form** should also be filled.





