Bisphosphonates for Prevention of Post-Denosumab Bone Loss in Premenopausal Women with Idiopathic Osteoporosis

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1. Study Purpose and Rationale

Osteoporosis in premenopausal women with normal menstrual function and no specific cause is termed idiopathic osteoporosis (IOP). IOP is a rare disease with an estimated prevalence of <200,000 affected premenopausal women in the United States. We recently completed an NIH-funded study of 64 premenopausal women with IOP, most with major osteoporotic fractures[1]. High resolution peripheral quantitative computed tomography (HR-pQCT), central QCT, and microCT of iliac bone biopsies documented that, compared to 40 normal controls, women with IOP have substantial microstructural deficits: thinner more porous cortices; fewer, thinner, more widely separated and heterogeneously distributed trabeculae; and markedly lower bone stiffness[2-4]. To determine whether teriparatide (TPTD), an osteoanabolic drug that increases bone formation, improved bone microarchitecture and strength in premenopausal women with IOP, we conducted an open-label, 24-month pilot study of TPTD, 20 µg daily, in 21 affected women. This study, published in 2013, revealed impressive gains in areal BMD (aBMD) by dual energy x-ray absorptiometry (DXA) at the spine (10.8 ± 6.4%), total hip (6.2 ± 5.7%) and femoral neck (7.6 ± 3.4%), and no significant change at the forearm[5]. Paired transiliac bone biopsies before and after TPTD revealed improved trabecular structure and a 71% increase in trabecular stiffness. Cortical thickness increased by 22% but cortical porosity also increased by 46%[5]. By HR-pQCT, trabecular structure and whole bone stiffness improved, despite a 17% increase in cortical porosity at the radius[6].

Most patients require antiresorptive therapy to maintain TPTD-induced increases in BMD. However, several studies have shown that BMD remains stable after TPTD is discontinued in postmenopausal women on estrogen[7-9] and in premenopausal women who regained normal menses after completing a course of nafarelin for endometriosis[10]. Based on these studies, we had previously hypothesized that the gains in BMD would be maintained in the IOP-TPTD pilot study participants because they were menstruating and estrogen replete. Therefore, we did not institute sequential antiresorptive therapy. However, contrary to our hypothesis, in 2015, we reported that participants in the pilot study sustained average losses of 4.8 ± 4.3% at the spine (p=0.0007), -1.1 ± 3.7% at the total hip and 1.5 ± 4.2% at the femoral neck over the 1-2 years after TPTD discontinuation[11].

In 2016, we completed enrollment of 41 premenopausal women with IOP into a randomized, 24-month, FDA Orphan Diseases Program-funded trial, “A Phase 2 Study of Teriparatide for the Treatment of Idiopathic Osteoporosis in Premenopausal Women” (FD003902; PI, Shane). Based on the follow-up data from our pilot study[11], we concluded that participants in FD003902 would require antiresorptive treatment to prevent bone loss after completing TPTD. To assess this, we are currently enrolling women into AAAN0161, an open-label, 24-36 month pilot study of denosumab (Prolia®, 60mg SC every 6 months). Denosumab is a potent antiresorptive drug that has been shown to increase BMD and reduce fracture incidence in postmenopausal women with osteoporosis. The denosumab study is also funded by the FDA Orphan Diseases Program (FD05114; PI, Shane). Only women who have completed FD003902 are eligible to participate in FD05114.

We selected denosumab because it is not retained in the skeleton and may thus be preferred by young women who may be contemplating future pregnancies. We hypothesized that denosumab, initiated in women who complete two years of TPTD in FD003902, would maintain or further increase central and peripheral areal and volumetric BMD, microstructure and stiffness in premenopausal women with IOP. We selected an open-label, observational design for FD05114 because FD003902 enrolled 41 women and some may not choose to participate; thus, power would be too low for a randomized, placebo-controlled design. The goals of the study are to estimate the effects of denosumab on central and peripheral, as well as trabecular and cortical, bone mass and microstructure and to obtain preliminary data to inform the design of a future randomized study.

Discontinuation of denosumab is followed by substantial increases in bone turnover markers to well above baseline, bone resorption reaching twice baseline levels for about 6 months[12,13]. Over the first 12 months off therapy, all the bone density gained on treatment is lost[12]. Since we began enrolling subjects in FD05114 (AAAN0161), several case reports and series have documented the occurrence of multiple vertebral fractures in some patients who have stopped denosumab[14-20]. Based upon these new fracture data, Amgen recently changed the Prolia label recommending that consideration should be given to transition to another antiresorptive drug in patients stopping denosumab. Therefore, all participants in AAAN0161 will be invited to participate in an extension study after they complete AAAN0161 (FD05114).

The primary goal of the study is to assess the extent to which bisphosphonate therapy will prevent decreases in bone mass that may occur after cessation of denosumab in premenopausal women with idiopathic osteoporosis (IOP) enrolled in AAAN0161 (FD05114) "Denosumab for the prevention of post-teriparatide bone loss in premenopausal women with idiopathic osteoporosis".

For the bisphosphonates, we have selected alendronate 70 mg weekly because bone density remained stable in 115 postmenopausal women who transitioned from denosumab to alendronate in the Denosumab Adherence Preference Satisfaction (DAPS) study[21]. However, in the DAPS study, compliance and persistence with alendronate was significantly lower than with denosumab [21] and some women have contraindications or intolerance to alendronate. Therefore, we have also included intravenous zoledronic acid 5 mg as an option. Zoledronic acid did not prevent bone loss in a case series of six women who received a single infusion 6 months after their last denosumab dose and had BMD measured 18-23 months later [22]; this timepoint reflects a combination of response to bisphosphonate and duration of response, but does not distinguish between the two. However, this may be because bone turnover would still have been very low 6 months after the last denosumab injection, and thus uptake of zoledronic acid to bone surfaces would have also been low at the time of the zoledronic acid infusion. For this reason, we will delay the initiation of zoledronic acid (and alendronate) until 6 months + 4 weeks (no later than 7 months) after the last denosumab injection. We selected the 6 month + 4 week time point based on Figure 4 of the paper by Bone et al. that indicated the bone resorption marker, C-telopeptide (CTX) exceeded baseline by 9 months after last dose[12].

The main goals of the new extension study are to estimate rates of bone loss during one year of bisphosphonate therapy (oral alendronate or intravenous zoledronic acid) initiated after completing denosumab. In addition, we will observe participants for a second year off bisphosphonate therapy to assess duration of response. We hypothesize that bisphosphonate therapy with alendronate or zoledronic acid, initiated after recovery of bone remodeling activity, will prevent significant bone loss after discontinuing denosumab. However, should there be significant bone loss during the first year of bisphosphonate therapy, defined as greater than the Least Significant Change (LSC) at spine or hip, and/or resulting in a T score $\leq$ -2.5), we would abrogate the proposed year of observation, and consider additional bisphosphonate therapy or reinstitution of denosumab, whichever we deemed most appropriate for the participant. Those who do not meet stopping criteria would continue to the second year of observation off bisphosphonates.

The rationale for conducting this study is as follows. The study is intended for premenopausal women who have completed 2 years of teriparatide and 2 to 3 years of denosumab and have responded well (BMD T or Z scores $\geq$ -1.5 at the spine) and for whom we could now consider a drug holiday because the risk of adverse effects of long-term antiresorptive therapy may be slightly higher after 5 years of continuous therapy. As stopping Prolia may result in loss of BMD gained on drug, an important goal of the study is to assess whether providing consolidation therapy with an oral or intravenous bisphosphonate will prevent that expected bone loss. Additional goals are to assess the effects of consolidation therapy on bone turnover markers and on bone quality as assessed by HR-pQCT, as well as on safety, specifically incident fractures and other adverse events. For those who remain at increased risk for fracture (BMD T or Z scores $\leq$ -1.5 at the spine and/or hip after 2 years of Forteo and 2 to 3 years of Prolia, or fragility fractures during therapy), continuation of denosumab would also be an option.

2. Study Design and Statistical Procedures

Women with IOP completing at least one year and up to three years of denosumab under AAAN0161 will be offered participation in an open-label study in which they would choose whether to take oral alendronate 70 mg weekly for 12 months or a single intravenous dose of zoledronic acid 5 mg.

Operationally, we propose to combine the final AAAN0161 visit and the initial Bisphosphonate Extension visit as follows. We will delay the final AAAN0161 visit by 4 weeks in order to permit partial recovery of bone remodeling activity before initiation of bisphosphonate therapy and to avoid a second visit soon after the final AAAN0161, as many of our participants travel long distances. Oral alendronate or intravenous zoledronic acid would be initiated 6 months plus 4 weeks after their last dose of denosumab. The transition from denosumab to bisphosphonate therapy will occur no later than 7 months after the participants' last injection of denosumab.

While a randomized controlled trial is the most rigorous design, and balancing the zoledronic acid and alendronate group size would be highly desirable, we do not believe that can achieve that without adversely impacting uptake of subjects from the parent study. Our experience indicates that many women in this age-group have specific concerns that influence their decision to take one or the other of the drugs. Some have relative contraindications to one or the other drug. We are concerned that if we require women to be randomized to zoledronic acid or alendronate, a substantial proportion may decline to enroll and thus be at risk for rapid bone loss and perhaps fractures. We feel that providing young women of childbearing potential with the ability to select the intervention that fits best with their particular clinical situation will increase recruitment and retention. In addition, the maximum number of women available to enroll in the extension study is 34. With only 17 subjects per group, power will likely be too low, even in a 1:1 randomized trial design, to detect between-groups differences, particularly with an active comparator design. In summary, we have selected an open-label design for three reasons:

1. The maximum number of women available to enroll in the extension study is 34. With only 17 subjects per group, power will likely be too low in a 1:1 randomized trial design to detect between-groups differences, particularly with an active comparator design.
2. Providing young women of childbearing potential with the abillity to select the intervention that fits best with their particular clinical situation will increase recruitment and retention.
3. This design will enable us to acquire data on the personal factors and beliefs that determine the participants' choice of intervention and will thus inform design of future studies involving young women with osteoporosis.

Statistical Analysis Plan

The main Specific Aim and main Hypothesis of this study are as follows:

In premenopausal women with IOP who have first completed two years of TPTD in FD003902 followed by 24-36 months of denosumab (Prolia®, 60mg SC every 6 months) and then complete 12 months of bisphosphonate therapy and 12 months of post-bisphosphonate observation, to estimate:

Aim 1: The percent change from baseline (bisphosphonate initiation) in areal BMD of the lumbar spine, total hip, femoral neck and one-third radius at 6, 12, 18 and 24 months after bisphosphonate initiation. The primary outcome will be percent change in lumbar spine areal BMD by DXA at 12 months. Exploratory outcomes will be the percent change in total hip, femoral neck and 1/3 radius areal BMD by DXA at 12 months as well as BMD changes at all sites at other timepoints.

Hypothesis 1: The gains in areal BMD by DXA that occurred on denosumab will be maintained at the spine, total hip and femoral neck during the 12 months of bisphosphonate therapy.

In the same population of women, we will address three Exploratory Specific Aims and one Safety Aim:

1. Estimate the percent change from baseline in total, cortical, and trabecular volumetric BMD, trabecular plate and rod microarchitecture, cortical porosity and stiffness of the distal radius and tibia by HR-pQCT and finite element analysis of HR-pQCT datasets at 12 and 24 months.

2. Estimate the AUC and percent change in the resorption marker, C-telopeptide from baseline (at 6, 12, and 18 and 24 months), and associations between C-telopeptide at bisphosphonate initiation and change in C-telopeptide after bisphosphonate initiation, and changes in areal and volumetric BMD, microarchitecture and stiffness.

3. Estimate the relationship between baseline and teriparatide-stimulated bone formation rate on the quadruple-labelled transiliac crest bone biopy obtained during "A Phase 2 Study of Teriparatide for the Treatment of Idiopathic Osteoporosis in Premenopausal Women" (FD003902; PI, Shane) and change in BMD of the lumbar spine, total hip, femoral neck and one-third radius after 12 months of bisphosphonate therapy and 12 months of post-bisphosphonate observation.

4. Delineate the incidence of adverse events, including vertebral and non-vertebral fractures, and episodes of abnormal serum calcium based on safety labs collected at each study visit.

Expected Results: After stopping denosumab, it is well-established that bone remodeling increases and BMD by DXA declines[12,13]. In addition, over the past two years, there have been several publications describing vertebral fractures in postmenopausal women stopping denosumab [14-20]. More recently, it has been appreciated that there is a small but significant imbalance in the incidence of multiple vertebral fractures after discontinuation of denosumab in a comparison between those completing denosumab versus those completing placebo. One risk factor for this outcome was the presence of vertebral fractures prior to therapy. This is of particular concern for women with IOP participating in AAAN0161 because a substantial proportion came to medical attention because of multiple vertebral fractures. There are no published data on the effects of stopping denosumab on BMD, bone turnover and fractures in premenopausal women stopping denosumab. This study will be the first to examine the effect of alendronate or zoledronic acid during the first year of withdrawal from denosumab in premenopausal women. Bone density remained stable in 115 postmenopausal women who transitioned from denosumab to alendronate in the Denosumab Adherence Preference Satisfaction (DAPS) study [21]. Zoledronic acid provided only partial protection from bone loss in a case series of six women who received a single infusion 6 months after their last denosumab dose and had BMD measured 18-23 months later [22]. However, this may be because bone turnover would still have been very low 6 months after the last denosumab injection, and thus uptake of zoledronic acid to bone surfaces would have also been low at the time of the single zoledronic acid infusion.

Because we will delay the initiation of zoledronic acid (and alendronate) until 6 month + 4 weeks after the last denosumab injection, a time when we expect CTX to be returning toward pre-denosumab concentrations [12], we expect that both oral and IV bisphosphonate therapy will prevent clinically significant bone loss (defined as greater than the Least Significant Change (LSC; see Section 3.C., 3.C.1) at spine or hip, and/or resulting in a T score $\leq$ -2.5) during the first year after denosumab is stopped. Should there be significant bone loss during the first year of bisphosphonate therapy, defined as greater than the Least Significant Change (LSC) at spine or hip, and/or resulting in a T score $\leq$ -2.5), we would discuss the findings with the participant and evaluate whether to abrogate the proposed year of observation. We would consider additional bisphosphonate therapy or reinstitution of denosumab, whichever we deemed most appropriate for the participant and was consistent with their wishes. Those who do not meet these criteria would continue to the second year of observation off bisphosphonates.

ANALYSIS PLAN

Sample Size Considerations

For this Bisphosphonate Extension Study, given the number of women who have completed FD003902 and who have initiated denosumab (n=25) and the number who remain on FD003902 (n=9), we anticipate that a maximum of 34 and a minimum of 30 women would enroll in the Bisphosphonate Extension Study.

Primary and Exploratory Outcome Variables

Aim 1: In subjects who stop denosumab therapy and complete 12 months of bisphosphonate therapy and 12 months of post-bisphosphonate observation:

Primary outcome variable: By DXA, the within-group difference (% change) in BMD at the

- Lumbar spine (L1-4) between the final Denosumab/Bisphosphonate initiation visit (DB baseline) and the 12-month bisphosphonate visit

Exploratory DXA outcome variables:

The within-group difference (% change) in BMD by DXA at the

- Lumbar spine (L1-4) between the final Denosumab/Bisphosphonate initiation visit (DB baseline) and the 24-month visit
- Lumbar spine (L1-4) between the 12-month bisphosphonate visit and the 24-month visit
- Total hip, femoral neck and 1/3rd radius aBMD between the final Denosumab/Bisphosphonate initiation visit (DB baseline) and the 12-month bisphosphonate visit
- Total hip, femoral neck and 1/3rd radius aBMD between the final Denosumab/Bisphosphonate initiation visit (DB baseline) and the 24-month visit
- Total hip and femoral neck radius aBMD between the 12-month bisphosphonate visit and the 24-month visit

Other exploratory outcome variables:

1. By HRpQCT, the within-group difference (% change) between the final Denosumab/Bisphosphonate initiation visit (DB baseline) and the 12- and 24-month bisphosphonate visit in
    a. Trabecular volumetric density of the distal radius and tibia
    b. Total volumetric density and trabecular number of the distal radius and tibia
    c. Trabecular plate and rod number by ITS of HR-pQCT datasets
    d. Cortical density, thickness, and porosity of the distal radius and tibia
    e. Whole bone stiffness of the distal radius and tibia by FEA of HR-pQCT scans

2. The within-group difference (% change) in serum C-telopeptide from the final Denosumab/Bisphosphonate initiation visit (DB baseline) and the 12 month bisphosphonate visit as well as the 12 month observation off bisphosphonate visit; the within-group difference in the net Area Under the Curve (AUC) during the first 12 months of bisphosphonate therapy and the second 12 months of observation off bisphosphonate therapy

3. The association between baseline and teriparatide-stimulated bone formation rate during FD003902; and percent change in aBMD by DXA of the lumbar spine, total hip, femoral neck and one-third radius between the Denosumab/Bisphosphonate initiation visit and the 12- and 24-month bisphosphonate visit

Safety outcome variables:

1. Number of incident vertebral fractures
2. Number of incident nonvertebral fractures
3. Number of episodes of abnormal serum calcium

Analysis: the main analyses will be to assess whether there are within-group differences between baseline versus 12 months during the 12 months of bisphosphonate treatment and between 12 months versus 24 months during the 12 months of observation after bisphosphonate treatment. We will conduct an exploratory between-groups analysis comparing rates of bone loss in subjects who choose alendronate versus those who choose IV zoldedronic acid. Finally, we will conduct an exploratory analysis to assess whether there are between-group differences between subjects who discontinue denosumab and receive bisphosphonate treatment for 12 months and 15 IOP subjects (historical controls) who completed 24 months of teriparatide without consolidation therapy and sustained average losses of 4.8 ± 4.3% at the spine (p=0.007), -1.1 ± 3.7% at the total hip and -1.5 ± 4.4% at the femoral neck by 2 years after TPTD discontinuation[11].

POWER ANALYSIS

For the Analysis, the primary analysis is the within-group analysis to assess whether there are differences in primary and exploratory DXA outcomes in bisphosphonate-treated patients at 12 and 24 months after cessation of denosumab (baseline). We expect to have a sample size of 30 subjects who agree to take bisphosphonate therapy after completing denosumab therapy. Using a two-tailed one-sample t-test and the largest SD (4.30%) for change in spine aBMD that we observed both in our historical cohort and in women with IOP who discontinued teriparatide[11], and given a sample size of 30 subjects who stop denosumab and take bisphosphonate therapy, a 3% margin and a 4.30% SD, we will have 98% power (the bisphosphonate within-group analysis), to estimate the confidence interval for an absolute change in aBMD at the spine (primary outcome), total hip and femoral neck (exploratory outcomes) in women who discontinue denosumab and take bisphosphonate therapy.

STATISTICAL METHODS

Given the non-randomized nature of this study, the primary objective will be to estimate the change in aBMD by DXA at the lumbar spine (primary), total hip and femoral neck (exploratory) after cessation of denosumab treatment. The main analysis is the **within-group difference analysis**: A one-sample two-tailed T-test against the null hypothesis of no change will be used to assess whether bisphosphonate treated patients differ on DXA outcomes relative to the measurements acquired at the cessation of denosumab.

3. Study Procedures

3.A. Calcium and Vitamin D, Fractures

All participants under protocol AAAN0161 are currently receiving calcium and multivitamin supplements. Supplements will continue to be provided during the new study: a daily multivitamin that contains 400 IU of vitamin D and very little or no calcium and a calcium supplement (Citracal +D), which contains 315 mg calcium and 250 IU vitamin per caplet. They will be instructed to take 2 Citracal +D daily (630 mg calcium and 500 IU vitamin D in total). Thus their total vitamin D intake from supplements will be 900 IU daily.

FRACTURES: We will capture all incident fractures by structured interview at each visit. Incident clinical and morphometric vertebral fractures will be ascertained by Spine X-rays at baseline,12 and 24 months. All subjects are instructed to notify their study team if they sustain a clinical vertebral fracture or a nonvertebral fracture. In addition, subjects will be specifically queried about incident fractures at each visit. All nonvertebral fractures will be verified by review of radiographs or radiograph reports.

3.B. STUDY PROTOCOL (Table 2)
Schedule of Visits

Visit 1 (Month 0): Enrollment Visit /Denosumab Cessation/ Bisphosphonate Initiation:

a. Oral inspection to assess for osteonecrosis of the jaw (ONJ)
b. Pregnancy testing
c. Imaging: DXA, VFA, Spine Radiographs, HR-pQCT
d. Laboratory assessments - plasma/serum collection
e. Administration of IV zoledronic acid 5 mg or dispensation of alendronate 70 mg weekly

Visit 2 (Month 6):

a. Oral inspection to assess for osteonecrosis of the jaw (ONJ)
b. Pregnancy testing
c. Imaging: DXA
d. Laboratory assessments - plasma/serum collection
e. Dispensation of alendronate 70 mg weekly

Visit 3 (Month 12):

a. Oral inspection to assess for osteonecrosis of the jaw (ONJ)
b. Pregnancy testing
c. Imaging: DXA, Spine Radiographs, HR-pQCT
d. Laboratory assessments - plasma/serum collection

Visit 4 (Month 18):

a. Oral inspection to assess for osteonecrosis of the jaw (ONJ)
b. Pregnancy testing
c. Imaging: DXA
d. Laboratory assessments - plasma/serum collection

Visit 5 (Month 24):

a. Oral inspection to assess for osteonecrosis of the jaw (ONJ)
b. Pregnancy testing
c. Imaging: DXA, Spine Radiographs, HR-pQCT
d. Laboratory assessments - plasma/serum collection

Table 2: Visit Protocol

	Protocol Review/ Informed Consent	Safety Labs	*Fractures and Adverse Events*	Pregnancy Testing *and Oral Exam*	BP	Spine X-rays, HR-pQCT	DXA	*Serum* for PTH, BTMs
Visit 1	X	X	X	X	ZA or ALN	X	X	X
Visit 2		X	X	X	ALN		X	X
Visit 3		X	*X*	X		X	X	X
Visit 4		*X*	*X*	X			X	X
Visit 5		X	*X*	X		X	X	X

Recruitment:. We will inform subjects of the option to enroll in the Bisphosphonate Extention Study before enrolling in AAAN0161 or during AAAN0161, as dictated by the time of their participation. We will discuss study protocol, risks and benefits prior to their final visit of the denosumab study. The Bisphosphonate Extension study will include only those subjects who have completed FD003902 and at least one year of Denosumab treatment.

3.C. Study Procedures

3.1. BMD by DXA: BMD (aBMD) of the LS (L1-4), right proximal femur and non-dominant forearm will be measured on Hologic QDR Discovery densitometers (Hologic, Inc., Waltham, MA). At CUMC and Creighton, dedicated, licensed x-ray technicians with long-term research experience perform all scans. Phantoms are scanned daily to check for detector drift and the results are appended to a quality control (QC) database. Results are downloaded to specific project databases. QC procedures include circulation of phantoms biannually. At CUMC, precision is 0.86% for the LS (LSC 2.4%), 1.36% for the FN (LSC 3.8%), and 0.70% (LSC 1.5%) for the 1/3 radius. At Creighton, precision is 0.94% (LSC 2.6%) for the LS, 1.40% for the FN 3.9) and 1.62% (LSC 2.6%) for the 1/3 radius. In terms of absolute BMD changes, the LSCs reported by Hologic are 0.022 g/cm^2 at the spine, 0.027 g/cm^2 at TH, 0.029 g/cm^2 at the FN and 0.023 g/cm^2 at the 1/3 radius. Radiation exposure for DXA of the spine, hip and forearm with the Hologic Discovery machine is 7.45 μSv.

3.2. Lateral (only) Spine Radiographs: Lateral spine radiographs at the lumbar and thoracic spine will be performed at New York Prebsyterian Hospital and Creighton University Medical Center according to standard techniques because VFA can sometimes miss fractures in the upper thoracic spine and because the

ascertainment of vertebral fracture is of such important in this particular group of patients. Radiation exposure for thoracic spine radiographs is 300 μSv and for lumbar spine radiographs is 200 μSv.

3.3. High Resolution Peripheral Quantitative Computed Tomography (HR-pQCT): HR-pQCT is performed on the XtremeCT II (Scanco Medical AG, Switzerland). The nondominant distal radius and tibia are immobilized in a carbon fiber shell (158-160). The region of interest (ROI) is defined on a scout film by manual placement of a reference line at the endplate of the radius or tibia; the first slice is 9.0 mm and 22.0 mm proximal to the reference line at the radius and tibia respectively. A stack of 168 parallel CT slices is acquired at the distal end of both sites (68kVp effective energy, 900 μA current, 43 ms integration time) with a nominal isotropic resolution of 60.8 μm. This provides a 3D image of 10.2 mm in the axial direction. Attenuation data are converted to equivalent hydroxyapatite (HA) densities. The European Forearm Phantom is scanned regularly for quality control. Scans are manually scored for motion on a scale of 1 (no motion) to 5 (significant blurring of the periosteal surface, discontinuities in the cortical shell, or streaking in the soft tissue). Images with motion score of 4-5 are excluded from analyses. We recently acquired the 2nd generation HR-pQCT scanner that has a higher resolution and thus permits direct quantification of virtually all microstructural indices that previously had to be derived. For HRpQCT of the forearm and leg, the estimated local average skin dose is 5 μSv per scan, and the effective whole body dose is below 5 μSv per scan, since only a very small fraction of the distal forearm or leg is irradiated.

3.4. Biochemical and Hormonal Assays

Safety: At each study visit, fasting morning blood samples for basic metabolic panel, including serum calcium, will be collected and processed at a commercial laboratory (Quest Diagnostics, Teterboro, NJ).

Mineral Metabolism and Bone Turnover: Fasting morning plasma/serum will be collected at CUMC, and at Creighton. Specimens will be shipped frozen from Creighton University to CUMC, aliquoted and frozen at -80° for batch analysis in the Biomarker Core of the Irving Institute for Clinical and Translational Research (CUMC CTSA), under the direction of Serge Cremers, PhD., PharmD. All assays are currently in place and inter- and intra-assay precision values are given in brackets after each test.

PTH is measured by a well-established total intact PTH IRMA (Scantibodies Laboratory, Inc., Santee, CA; 6.8%, 4.8%)**, serum calcium** by colorimetric assay (Cobas Integra 400 Plus, Roche Diagnostics, Indianapolis, IN; 3.5%, 0.99%), C-telopeptide (**CTX**) by CLIA (Immunodiagnostic Systems, Scottsdale AZ; 6.3%, 3.2%), **25-OHD** by RIA (Diasorin RIA, Stillwater, MN; 10.5%, 8.2%).

4. STUDY DRUGS OR DEVICES

Alendronate or zoledronic acid will be provided to subjects at no cost. Both medications will be stored and dispensed by the research pharmacies at Columbia and Creighton Universities according to standard, IRB-approved procedures. CUMC will be the primary Research Pharmacy and will ship study drug to Creighton University for subjects enrolled at Creighton. Zoledronic acid (5 mg, open label) will be administered to participants once by intravenous injection performed according to standard procedures by licensed providers at Columbia University (in the Irving Institute Center for Translational Science or CTSA) and Creighton University.

5. STUDY SUBJECTS

INCLUSION/EXCLUSION CRITERIA:

Inclusion Criteria: All women completing at least 12 months of Forteo treatment under FD003902 and at least 12 months of denosumab under AAAN0161 who remain without a diagnosis of an excluded medical condition and medication exposures as detailed below, will be offered enrollment into this study. Women who transitioned into menopause during FD003902 were excluded from participation in AAAN0161 as this could affect the results of the study. Women who transition into menopause during the denosumab study will be permitted to participate in this Bisphosphonate Extension Study.

Exclusion Criteria:

1) Known intolerance to calcium supplements
2) Contraindications to bisphosphonate treatment:
    a. Hypocalcemia
    b. Pregnancy
    c. Known hypersensitivity to bisphosphonates
3) History of osteomalacia
4) History of osteonecrosis of the jaw
5) History of dental extraction or other invasive dental surgery within the prior 4 weeks
6) Invasive dental work planned in the next 12 months
7) Any condition or illness (acute, chronic, or history), which in the opinion of the Investigator might interfere with the evaluation of efficacy and safety during the study or may otherwise compromise the safety of the subject
8) Self-reported or known alcohol or drug abuse within the previous 12 months
9) Current or recent (within 1 year of enrollment) inflammatory bowel disease or malabsorption
10) Abnormal laboratory tests performed during Visit 1 (see below under STUDY PROTOCOL)
    a. Renal insufficiency or liver disease: eGFR < 35 ml/min, AST/ALT >50% above upper limit of normal
    b. Hypercalcemia, hypocalcemia
    c. Vitamin D deficiency: 25-OHD < 30 ng/mL

Subjects must be willing to participate voluntarily. Specifically excluded are the following: 1) women less than 20 (or 35 in the case of those who wish to participate because they have low BMD); 2) protected individuals (institutionalized); 3) prisoners; 4) any other prospective participant who, for any reason, might not be able to give voluntary informed consent.

Creighton University is a collaborating site. At Creighton University, Drs. Robert Recker and Joan Lappe will recruit subjects and perform the same studies as proposed for Columbia University.

6. RECRUITMENT

Patients for the study will be recruited from those subjects who have completed FD003902 and at least one year of AAAN0161. The Principal Investigators, Dr. Shane and Dr. Cohen, Co-investigators, Dr. Recker, and Dr. Lappe, and Research Coordinators, Mrs. Bucovsky, Ms. Kamanda-Kosseh and Mrs. Stubby, will be directly responsible for enrolling subjects and obtaining consent for the study. Permission will be first obtained from the patients' primary care physician, if appropriate. Written consent will always be obtained according to appropriate Informed Consent forms that will be reviewed and approved by the Institutional Review Boards of the both institutions. Each patient is counseled at the time of enrollment that all aspects of the study are separate from their management as a patient with osteoporosis. They are assured that participation is entirely voluntary and that refusal to participate in the study will not in any way influence their care. Statements to this effect will be included in all Informed Consent forms, which will be signed by the investigator obtaining consent and by the subject in the presence of a witness.

7. INFORMED CONSENT PROCESS

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

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

8. CONFIDENTIALITY

Dr. Elizabeth Shane is Principal Investigator of this protocol and is also the Sponsor.

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

Information obtained in the setting in this study may be made available to the following entities:
- The Sponsor-Principal Investigator, co-investigators, study staff and other health professionals who may be evaluating the study
- Columbia University
- New York Presbyterian Hospital
- Authorized representatives of the Food and Drug Administration ('FDA'), the Office of Human Research Protections ('OHRP') or other government regulatory agencies
- Applicable Institutional Review Boards ('IRBs') that independently review the study to assure adequate protection of research participants, as required by federal regulations.

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

9. PRIVACY PROTECTIONS

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

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

Our safety reporting responsibilities require the investigator to report any adverse events to the IRB, and the FDA. These reports will include only a study ID, and will not divulge the participant’s identity.

10. POTENTIAL RISKS
The risks of this study are related to the venipuncture, radiation exposure and the study medication, alendronate/ zolendroic acid.

Venipuncture: The risks of venipuncture for blood drawing include pain, bleeding, bruising, and a remote possibility of infection or inflammation at the site. Additionally, there is a possible risk of syncope in individuals

who are prone to vasovagal responses. To minimize these risks, trained phlebotomists who follow proper technique perform all venipunctures.

Radiation: Radiation exposure for DXA of the spine, hip and forearm with the Hologic Discovery machine is 7.45 μSv. This is about the amount the average person receives from background radiation in 1 day. For HRpQCT of the forearm and leg, the estimated local average skin dose is 5 μSv per scan, and the effective whole body dose is below 5 μSv per scan, since only a very small fraction of the distal forearm or leg is irradiated. Radiation exposure from the lateral thoracic and lumbar spine radiographs is 300 μSv and 200 μSv, respectively. Based on these data, we estimate the following radiation exposure for participation in this clinical trial, primarily driven by the spine x-rays, is 1550 μSv, approximately half the 2400-3600 μSv of natural background radiation received in a year.
For purposes of comparison, there is 60 μSv radiation associated with a round-trip transcontinental plane flight. The amount of radiation from exposure associated with a standard abdominal/pelvic or chest CT scan is 7,000-10,000 μSv. Expressed as equivalencies to background radiation, a standard mammogram is associated with radiation exposure equivalent to approximately 2 to 3 months of natural background radiation. A standard abdominal or chest CT scan is associated with radiation exposure equivalent to approximately 15-22 months of natural background radiation. We will counsel all study subjects about the total amount of radiation that they will receive as a result of participation as part of Informed Consent procedures of that particular study. In addition, they will be counseled that radiation exposure is cumulative throughout life and any additional exposure should be considered carefully.

Placement of an Intravenous Line for Zoledronic acid infusion: Placing an IV may cause some redness, bruising, swelling, bleeding, discomfort or pain at the spot where the needle enters the body. Although rare, infection may also occur. Some people may experience dizziness, lightheadedness and/or fainting. The IV will be removed once the infusion has been completed.

Zoledronic acid: Zoledronic acid is contraindicated in individuals with hypocalcemia; creatinine clearance less than 35 mL/min and with evidence of acute renal impairment; and hypersensitivity to any component of zoledronic acid. Participants with any of these characteristics will not be eligible to receive zoledronic acid.
There are several potential risks of zoledronic acid.
Hypocalcemia may worsen during treatment so participants must be adequately supplemented with calcium and vitamin Renal impairment may develop, particularly in patients with underlying renal impairment or with other risk factors, such as advanced age or dehydration. For this reason the dose will not exceed 5 mg and the duration of infusion will be no less than 15 minutes. Creatinine clearance will be measured before the dose, which will be withheld if < 35 ml/min
Osteonecrosis of the Jaw (ONJ) has been reported. All participants will have a routine oral exam by the prescriber prior to treatment.
Atypical Femur Fractures have been reported. Patients with thigh or groin pain will be evaluated to rule out a femoral fracture
If given during pregnancy, Zoledronic acid can cause fetal harm. All participants of childbearing potential will be advised to use effective contraception for 12 months after the zoledronic acid infusion.
Severe bone, joint, and muscle pain may occur and there may be a rise in body temperature (fever) in the 24 to 72 hours following the first dose of study medication. These symptoms may last up to three days and usually do not come back. All participants will be instructed to drink plenty of fluids and to take acetaminophen every 6 hours the day of and the day following the infusion.

The most common adverse reactions to zoledronic acid (greater than 10%) are pyrexia, myalgia, headache, arthralgia, pain in extremity flulike illness, nausea, vomiting, diarrhea and eye inflammation.

Alendronate: Alendronate is contraindicated in individuals with abnormalities of the esophagus which delay emptying such as stricture or achalasia; inability to stand/sit upright for at least 30 minutes; at increased risk of aspiration; hypocalcemia; hypersensitivity to any component. Participants with any of these characteristics will not be eligible to receive alendronate.

Potential risks of alendronate include severe irritation of upper gastrointestinal (GI) mucosa; worsening of hypocalcemia; bone, joint, muscle pain; osteonecrosis of the jaw; and atypical femur fractures. The most common adverse reactions (≥3%) are abdominal pain, acid regurgitation, constipation, diarrhea, dyspepsia, musculoskeletal pain, and nausea.

11. DATA AND SAFETY MONITORING

A Data & Safety Monitoring Board has been established for the parent TPTD study (FD003902) and the denosumab study will be invited to continue for the Bisphosphonate Extension Study to ensure continuity. The DSMB will monitor subject accrual, ethical conduct of research, as well as oversee adverse events and any unforeseen consequences in the study population. The DSMB is chaired by Dr. Mishaela Rubin, an endocrinologist and Associate Professor of Medicine at CUMC with expertise in osteoporosis and clinical trials, Dr. Judith Korner, an endocrinologist and Professor of Medicine at CUMC outside of the field of metabolic bone diseases (obesity and weight control), and a statistician, Dr. Emelia Bagiella, Professor of Health Evidence and Policy at Mount Sinai Medical School in New York City. The DSMB is independent of all study personnel, and has signed a conflict of interest form to that effect. It meets annually face-to-face and by conference call as necessary in case of complications or issues. The DSMB may recommend any steps necessary to protect the participants.

Interim Analysis: No efficacy interim analysis is planned. The proposed recruitment of a modest number of subjects, with the anticipated recruitment schedule, diminishes the need for an interim efficacy analysis. However, this decision will be reviewed at the first meeting of the DSMB. If the DSMB decides that an interim efficacy analysis is necessary, we will amend the protocol according to their decision.

Stopping Rules: Stopping rules will be invoked if new information emerges making the questions in this proposal moot or new information provides evidence suggesting that the use of bisphosphonates in premenopausal women with IOP is contraindicated. Stopping rules will be invoked in individual participants if there is significant bone loss during the first year of bisphosphonate therapy, defined as greater than the Least Significant Change (LSC) at spine or hip, and/or resulting in a T score $\leq$ -2.5). If this amount of bone loss is documented, we will albrogate the proposed year of observation, and consider additional bisphosphonate therapy or reinstitution of denosumab, whichever we deemed most appropriate for the participant. Those who do not meet stopping criteria would continue to the second year of observation off bisphosphonates.

Protocol Modifications: The IRB must review and approve any protocol amendment. Modifications will not be undertaken without notification of the IRB, the DSMB, Amgen and the FDA.

Reporting: All adverse events will be reported according to the guidelines set forth by the FDA and applicable IRBs. We commit to follow the FDA reporting requirements set forth in the Code of Federal Regulations Title 21, Section 312.32, which is summarized below.

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

Dr. Shane, the Sponsor/Principal Investigator, shall also notify the FDA and Amgen by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but in no event later than *7 calendar days* after the the Sponsor/Principal Investigator's initial receipt of the information. Each telephone call or facsimile transmission to FDA shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product

review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND.

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

Dr. Shane, the Sponsor/Principal Investigator will meet all safety reporting obligations as outlined in the contract with Amgen.

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

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

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

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

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

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

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

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

16. Sponsor Responsibilities

Dr. Elizabeth Shane, the Principal Investigator is the sponsor of and is legally responsible for the legal and regulatory compliance of this study. Study compliance and subject safety will be monitored periodically by the sponsor-principal investigator, Dr. Elizabeth Shane. The task of overseeing subject safety will be the responsibility of the DSMB, sponsor-principal investigator and study investigators. Adverse events and/or unanticipated problems will be reported to the Columbia IRB in accordance with their policy, to Amgen and to the FDA in accordance with their reporting guidelines (see Section 11.0 for more detailed information). Study compliance and assurance that the study is conducted in accordance with the protocol will be facilitated by a protocol and operations manual developed by the investigator. Participating research personnel will be instructed in proper forms completion and electronic data entry procedures, as it is applicable to their study role. Adherence with the study protocol and recruitment goals will be monitored by the sponsor-principal investigator on an ongoing basis, with monthly conference calls made to participating sites (Creighton University). Upon identification of incomplete reports or missing data, this information will be obtained from the study site in writing.

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

Records and documentation pertaining to the protocol will be kept in the protocol regulatory binder and online through the Columbia RASCAL system. Subject specific records will be stored in a password protected database or in a locked cabinet to ensure privacy and confidentiality, as is detailed in Sections 8.0 and 9.0. Data entry will be ongoing throughout the course of the protocol so that interval reports to the investigators, IRB, Amgen and other regulatory bodies are readily accessible.

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