Study Protocol

Official Title: Zoledronic Acid for Osteoporotic Fracture Prevention (ZEST II)

ClinicalTrials.gov ID (NCT number): NCT02589600

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Scientific Background

Impact of Osteoporosis and Fractures in Long-Term Care Residents:
Osteoporosis is devastating, particularly for the elderly. Each year 250,000 Americans suffer a hip fracture, of whom 20% die in the subsequent year, 25% are institutionalized, and ≤50% fully recover. Because the fastest-growing segment of the U.S. population is women >85 years, and 1/3 of those who fracture are over age 90, the number of patients with hip fractures will double in the next 15 years (1,2) and the current annual cost of $17 billion will double by 2040 (3). Osteoporosis' impact for America's 2 million long-term care (LTC) residents is even more dramatic, with a prevalence of 85% (4) and an 11% annual incidence of nonvertebral fractures. Such residents were hospitalized ≥15 times as often as those without fracture (5) and those with hip or vertebral fractures are at 2-3x greater risk for future fracture (6,7). A vertebral fracture is associated with back pain (8-11), decreased mobility, increased bed rest (12), and higher rates of hospitalization and mortality (13,14). A recent review of 60,000 nursing home patients reported that following a hip fracture, 36% died and 53% died or developed new total dependence in 6 months (15).

Osteoporosis Therapy in the Elderly:
Osteoporosis Therapy is Safe and Efficacious in Healthy Elderly: The PI reported on the first prospective, randomized, placebo-controlled, multi-center trial of daily bisphosphonate therapy in healthy LTC residents (16). At 2 years, spine and femoral neck bone density had increased by 4.4% and 3.2%, respectively, with the bisphosphonate alendronate. This study demonstrated that daily alendronate was safe, well-tolerated, and improved bone mass in independent, ambulatory, cognitively intact women, able to take a daily oral bisphosphonate by themselves. The study excluded women with multiple medical problems, limited mobility, cancers, cognitive impairment, or diseases that impact bone and did not address the question if such therapy was safe or efficacious in institutionalized elderly.
Post-hoc pivotal trial subgroup analyses comparing those >75 to those <75 years suggest zoledronic acid (17), teriparatide (18) and denosumab (19) are efficacious in older very healthy women who qualify for a clinical trial. These trials only included women who were healthy, cognitively intact, fully ambulatory, and able to sign their own consent. Fracture reduction data in frail elderly are lacking.

Osteoporosis Therapy in Frail Elderly may not be Clinically Effective:
There are little data on frail elderly or non-healthy LTC residents (20,21). In addition, the limited available data questions the efficacy of bisphosphonate in frail elderly. For example, in the HIP study, fracture reduction was not demonstrated with an oral bisphosphonate in women over age 80 enrolled based on clinical risk factors only (22). Furthermore, the PI's ZEST study in frail LTC residents, demonstrated improvement of BMD at the hip and spine with zoledronic acid, however no fracture reduction trend was observed. The majority of these patients were cognitively impaired, sedentary and had multiple comorbid conditions, excluding them from an industry trial. Fracture reduction data are lacking in these vulnerable patients. The March 2011 NIH/ASBMR Forum on Aging and Skeletal Health echoed the critical need for osteoporosis research, a fracture reduction study and treatment for frail LTC residents (23).

Why would therapy fail in frail elderly? Both skeletal and nonskeletal factors in frail elderly may mask a fracture reduction benefit from a potent bisphosphonate. Despite the improvement in bone density and reduction in bone turnover (both independent contributors to fracture reduction), frail individuals may not benefit due to severely compromised skeletal integrity from poor trabecular connectivity (disconnected rods and plates), increased trabecular fragments,

perforations in trabecular and cortical bone, impaired microstructure, or unhealed stress fractures (24-27). This concept was hypothesized by Parfitt (28,29). Bisphosphonates can't reconnect broken fragments. Alternatively, nonskeletal factors may contribute to lack of benefit including minimal mobility (less weight bearing) or short life expectancy (too short to see a benefit), in addition to other factors such as increased falls (27). Our previous ZEST 1 study was not powered to examine fracture reduction. However, neither the limited statistical power nor the point estimates observed can be used to infer that fracture reduction would or would not be seen in a larger study (30); strong computational evidence suggests that only a fracture reduction study will suffice. Based on our data demonstrating a positive impact on both bone mass and bone turnover, we believe a fracture reduction study is justified and essential.

Study Objectives

Primary Outcome:
Effectiveness of fracture reduction will be demonstrated by total non-traumatic incidental fractures (vertebral and nonvertebral [identified by x-ray, CT, MRI, VFA imaging) except those viewed as severe trauma (fall from a height higher than a stool or chair or severe trauma other than a fall), cancer-related or fractures of the toes, finger or facial bones. Incident morphometric vertebral fractures will be defined using the Genant criteria (134) as a reduction in vertebral height of at least 20% by quantiative morphometry or by an increase of one severity grade or more on semiquantitative analysis (134, 135). We will be able to assess primary outcome in all randomized women, optimally obtaining partial data in terms of person months of exposure and corresponding counts of fractures for analysis from those expiring/dropping out/moving before 3 years.

Secondary/Exploratory Outcomes:
(1) New nonvertebral fractures
(2) New vertebral fractures

Other Secondary/Exploratory Skeletal Outcomes:
(1) Hip and Spine BMD
(2) Trabecular bone score (TBS)
(3) Markers of bone turnover (CTX and P1NP)

Laboratory Safety Outcomes:
(1) H&H
(2) Serum Calcium
(3) Albumin
(4) Alkaline phosphatase
(5) Serum 25 OH Vitamin D
(6) eGFR

Adverse Events Outcomes:
(1) All and serious adverse events, both by MedRA category and any-event basis
(2) All and serious acute phase adverse events ≤3 days from an infusion
(3) Special attention to falls, atrial fibrillation, stroke and symptomatic hypocalcemia

Study Design & Methods

This is a 3-year, randomized, double-blind, calcium and vitamin D controlled trial with the antiresorptive agent zoledronic acid (Reclast).

The study consists of 5 main visits (Screening, Randomization, Month 12, Month 24, and Month 36), with pre and post infusion safety check visits. Pre-infusion safety check visits will be done up to 2 weeks prior to receiving the annual IV study drug or placebo. Post-infusion safety check visits will be done 1-3 days after infusion.

We have chosen yearly intravenous zoledronic acid because it has been shown to significantly reduce vertebral fractures by 70%, all clinical fractures by 35%, hip fractures by 41% in the pivotal trial that included older healthy women. Additionally, in a sub-analysis including women ≥ 75 years old, yearly zoledronic acid decreased vertebral fractures by 66% over 3 years. Moreover, fracture reduction after 2 and 3 infusions were 47% and 39%, respectively. Because nursing home patients are difficult to treat and resources are limited, the intravenous injection has several advantages. It does not require fasting, administration at a specific time of day, or sitting up, which are all significant practical advantages over a weekly oral bisphosphonate. All patients without liver abnormalities will be offered acetaminophen prior to the infusion and for 2 days post-infusion to decrease acute phase reactions and maintain the blind.

Rationale for yearly dose versus single dose: Despite the improvement in density over 2 years after a single dose in our initial ZEST study, we will follow conventional yearly dosing that demonstrated fracture reduction in the pivotal trials. In the event we do not find a fracture reduction benefit, we wanted to be certain that it would not be due to under-dosing.

At the request of the DSMB, we will be offering a Follow-up Extension phase to this study to continue data collection on the skeletal health of participants in the ZEST II study. Therapy and blood work will not be provided throughout the follow-up extension. There will be a maximum of three visits in the follow-up extension. The number of visits that a participant will have can be determined by when they have completed their Month 36 visit. Participants who have completed the Month 36 visit on or before July 31, 2019 will have three follow-up visits. Participants who have completed the Month 36 visit on or before July 31, 2020 will have two follow-up visits. Participants who have completed the Month 36 visit on or before July 31, 2021 will have one follow-up visit. Participants who do not complete the Month 36 visit before August 1, 2021 will not be eligible to participate in the follow-up extension.

SKELETAL ASSESSMENTS

Fragility Fractures: From baseline to the end of follow-up, nonvertebral and clinical vertebral fractures will be identified by the electronic medical record alert and by Theradoc (a real-time, stand-alone clinical alert and decision support application used at UPMC LTC facilities, with custom rules to be written for this study to provide detection and identification of participants presenting to any UPMC facility so that generated alerts will be sent to the study team via e-mail). In addition, participants/charts will be queried at approx. 6 month intervals for clinical fragility fractures defined as a fracture following a fall from a standing or sitting height. All reported fractures will be verified by obtaining the radiology report confirming the fractures. We exclude fingers, toes, face, and skull fractures. All femur fractures will be examined for atypical fractures using ASBMR criteria (128).

Vertebral Fractures: We will use the presence of thoracic or lumbar vertebral fractures as determined by Vertebral Fracture Assessment (VFA is DXA-derived) as the primary classification of vertebral fracture performed annually (53, 73, 129). The fractures will be scored according to the method of Genant (130, 131) and considered a grade 1 mild vertebral deformity, a grade 2 moderate vertebral deformity, or a grade 3 severe vertebral deformity. We will assess vertebral fractures at baseline, 12, 24, and 36 months, as well as at follow-up visits 1, 2, and 3. Conventional x-rays or a MRI that demonstrates a fracture will also be used.
Indices of Bone Mineral Metabolism: Serum will be assayed for 25-hydroxyvitamin D2/D3 for the secondary aim. We will collect serum for bone turnover markers at baseline and M36 for responder analysis for the exploratory aim (60, 65-67, 132, 133). To assess bone resorption, we will measure serum CTX. We will assess bone formation with P1NP. Serum will be archived for future analyses.

Trabecular Bone Score (TBS): TBS, a new gray-level texture measurement is evaluated in the same region of interest as the spine BMD using the iNsight Software version 1.9 (54-58). TBS utilizes the 2-D DXA spine images and provides 3-D microarchitectural images and parameters (57, 59). The precision for TBS ranged from 1.1 to 1.9% (55). In previous studies, TBS was independent of BMD for fracture prediction and significantly improved risk protection (80, 81). TBS is only minimally affected by sclerosis/osteoarthritis (57). For the exploratory aim, we will examine TBS from DXA images.

Eligibility Criteria

Inclusion Criteria:

Our goal is to include older women with osteoporosis or low bone mass (with fracture risk) unless there is a known contraindication to therapy. We will enroll ambulatory women age ≥65 years including those using assistive devices to maximize generalizability, if they:
1) Reside in long-term care (LTC) including Managed Senior Communities which provide the following: (a) An environment engineered to prevent falls (handrails, ramps) and are ADA accessible; (b) Facilitate access to medical attention (pull cords, life-alerts, or other electronic means); (c) ADA accessible transportation services available; (d) Provide or coordinate meals; (e) Secure building (automatically locked door or buzzer system, security cameras).
2) Have a) osteoporosis by axial bone density (spine, hip or forearm BMD T-score ≤ -2.5 SD)(99,100); or b) a previous adult fragility fracture of the spine or hip; or, c) would be treated based on FRAX (101,102) NOF treatment thresholds of a 10 year risk of ≥ 20% for a major osteoporotic fracture or ≥ 3% for hip fracture using femoral neck BMD (103).

Follow-up Extension Inclusion Critera:
1) Complete Month 36 Visit on or before July 31, 2021.

Exclusion Criteria:

We will exclude:
1) Men because osteoporosis is less common in men and our initial ZEST 1 study only included women.
2) Institutionalized women with subacute illnesses surviving or discharged in < 3 years.
3) Women currently on bisphosphonate, denosumab, or teriparatide therapy or who have been on a bisphosphonate for greater than 1 year during the previous 2 years because bisphosphonates are long acting (104).
4) Patients with a calculated creatinine clearance < 35 ml/min (105,106) or who have a contraindication for bisphosphonates (allergy, hypocalcemia).
5) Women scheduled for a tooth extraction to avoid jaw osteonecrosis (107-109).

We will screen with a detailed history, chart review, and baseline laboratory analyses. Women with vitamin D levels <25 ng/mL (110,111) will be treated with vitamin D 50,000 IU/wk for 8 weeks (112,113). The patient will be enrolled if the follow-up vitamin D level is ≥ 25 ng/mL. Vitamin D levels <25 ng/mL are associated with falls (114,115) and our prior ZEST 1 Study data supports a level ≥ 25 ng/mL for better performance and improved walking (98). Patients can continue on glucocorticoids and anticonvulsants because their use is common (116). Women on raloxifene, calcitonin or using protective hip pads will be allowed to participate.

Exclusion Criteria #3, #4, and #5 will not apply to participants in the Follow-up Extension phase of this study.

Statistical Considerations

Overview: All statistical analyses will use SAS® version 9 (SAS Institute, Inc., Cary, North Carolina) based on intention-to-treat. First, appropriate descriptive statistics will be computed and graphical summarizations made for all variables for each treatment group for each time point as well as raw and percent change scores from baseline to obtain an overall sense of the distributional characteristics, missing values and general data quality. Second, baseline measures will be compared across arms using independent samples t- and a Wilcoxon rank sum tests, as appropriate, for continuous variables and chi-square and Fisher's exact tests, as appropriate, for categorical variables. Although no significant differences are expected due to randomization and large sample size, any variables found to be significantly different will be accounted for by including them as covariates in sensitivity analyses. Third, main analyses will be performed using a negative binomial regression model. Finally, exploratory analyses will be performed.

Main Analyses: First, we will fit a series of negative binomial regression implemented in the SAS® GENMOD procedure with each fracture outcome as the dependent variable; duration of follow-up as an offset to account for each participant's exposure; treatment arm as the main independent factor of interest; and any covariates deemed important as additional independent variables in sensitivity analyses. The incident rate ratio and its statistical significance at $\alpha=0.05$ level for the primary outcome of all new fractures will serve as a formal test of the main fracture reduction hypothesis (H1). Second, we will fit a series of linear mixed models using the SAS® MIXED procedure with raw and percent change each from baseline in each of the continuous outcomes representing laboratory measures related to safety as the dependent variable; treatment arm, follow-up time point (12-/24-/36-month, as available) and their interaction as the

fixed effects of interest; and a subject random effect. For some measures, we will fit simpler models (due to only one planned post-infusion assessment) using the GLM procedure with raw and percent change each as the dependent variable, and treatment arm as the main factor of interest. We will appropriately construct sets of contrasts to test various hypotheses of interest by comparing the said change over time between the two arms. Third, we will fit a series of logistic regression models using the SAS® LOGISTIC procedure with each incident dichotomous adverse event during the 36-month follow-up (any and specific types of adverse events) as the dependent variable, and treatment arm as the independent factor of interest. The resulting odds ratios and levels of significances will be used to test the specific hypotheses for Aim 2. We will repeat all main analysis after stratification by institutional setting (assisted living/nursing home).

Findings from the proposed trial will be most useful if (a) we can also identify a target sub-population of the long-term care that is most likely to benefit from zoledronic acid and/or least likely to experience side effects; and (b) we can speculate whether fracture reduction or non-reduction in women, despite improvement in BMD, depends on bone microstructure as measured by TBS. Therefore, using several techniques, some with an exploratory data mining philosophy, we will identify such sub-populations to address Aim 3(a). First, we will include all baseline clinical and laboratory characteristics, one-at-a-time, as an additional fixed effect in the models above, along with an interaction term with treatment group. Statistical significance of the interaction term will be interpreted as a patient baseline characteristic whose levels exhibit potentially differential treatment effects and/or safety profiles. Second, we will stratify analyses by such baseline criteria to actually obtain preliminary estimates of subgroup-specific treatment effects/safety differences. Third (data mining), using only the active arm, we will fit a series of logistic regression models using the SAS® LOGISTIC procedure and classification tree models using Salford Predictive Miner® software (Salford Systems, Inc., San Diego, California) with incident fracture as the dichotomous response variable; and baseline characteristics as predictors. Logistic models are more efficient when associations are linear, and hard-to-discover higher order interactions and non-linearity and/or multicollinearities among predictors do not exist, while classification tree models are more efficient when they do exist. Thus we will use both methods to obtain areas under the receiver operator characteristic curve (AUROCC) to quantify predictive accuracy, and use the results from the method with a greater AUROCC. For logistic regression we will use the backward elimination and for classification trees minimum misclassification-complexity cost tree to guard against overfitting. We will use the method of DeLong to obtain statistical significance of the differences in predictive accuracy between the models. For predicting improvements in continuous BMD change outcomes, we will employ a similar approach but with standard multiple linear regression and regression tree models and proportion of explained variance (R2) to quantify predictive accuracy.

For Aim 3(b), the association between zoledronic acid, BMD, TBS and fracture reduction will be explored in two ways. First, we proposed above to examine the effect of the study drug on TBS with standard linear models. Second, using only the active arm of the trial, we will fit a negative binomial model with number of fractures within 3 years as the dependent variable; and baseline BMD, 3-year change in BMD, baseline TBS, and 3-year change in TBS as independent variables. The statistical significance of regression coefficients for TBS measures will be interpreted as evidence supporting that fractures over a 3-year period depend on TBS and its changes over the same period independent of BMD.

Exploratory Analyses: We will perform exploratory analyses to assess the robustness of results and make more refined conclusions. For example, we will stratify adverse event and fracture

analyses to identify any differences between short- and long-term effects and/or within organ systems.