Sustaining Skeletal Health in Frail Elderly

NCT02753283

21 AUG 2024

Study Protocol PROUD

Overall summary: We propose to conduct a 2-year, randomized, double-blind, calcium-vitamin-D controlled trial to test the efficacy of the antiresorptive RANK ligand inhibitor, denosumab, among a cohort of 201 institutionalized, overlooked, under-served, frail men and women ≥65 years old in long-term care (LTC).

Our co-primary outcomes are percent changes in bone mineral density (BMD) of the total hip and spine over 24 months.

Informed consent: All participants or their responsible party will provide written informed consent for screening and then randomized if eligible.

Inclusion/Exclusion Criteria: Ambulatory male and female residents with osteoporosis or low bone mass (at risk for fracture) age 65 and older will be considered if:

1) They reside in long-term care (LTC) including Managed Senior Communities.

2) They have a) osteoporosis by bone density (spine, hip or forearm BMD T-score ≤ -2.5 SD) (108,109), b) a previous adult fragility fracture of the spine or hip, or c) would be treated based on FRAX and the NOF treatment thresholds of a 10-year risk of ≥ 20% for a major fracture or ≥ 3% for hip fracture using femoral neck BMD

We will exclude institutionalized residents with subacute illnesses who are not expected to survive or who will be discharged in < 2 years. Non-ambulatory residents (those who cannot stand and pivot with assistance in order to transfer to the DXA table) will be excluded. We will exclude those currently on therapy (including a bisphosphonate, denosumab or teriparatide) or who have been on a bisphosphonate for greater than 1 year during the previous 2 years because some bisphosphonates are long acting We will exclude subjects with a history of hypocalcemia or contraindication for treatment.

Intervention: Participants will receive denosumab 60 mg subcutaneous injection or matching placebo every 6 months for 2 years. Participants, study personnel and investigators are blinded to the treatment assignments. All participants will receive appropriate calcium and vitamin D supplementation based on the Bone Health Osteoporosis Foundation guidelines.

Assessments: The visits will be conducted in the participant's LTC facility and participants will be assessed every 6 months for 2 years.

Primary outcomes: The 24-month percent change in bone mineral density (BMD) of the spine and hip.

Randomization and Masking: We will use the high quality pseudo-random deviate generator in SAS® (SAS Institute, Inc., Cary, North Carolina) to randomize women and men separately to the two treatment groups in a 1:1 ratio. Within each gender, ambulatory status may play a role in a participant's bone integrity, and confound the comparison between groups. Therefore, we will further stratify the randomization scheme for each gender with respect to the level of assistance required for ambulation (with/without assistance except cane) to force a balance, by design, between the arms. Those non-ambulatory will be excluded. We will use a blocked randomization scheme to force a within-stratum balance between the numbers of subjects in each arm at any point during the recruitment period, and employ a blocking strategy with random block sizes. Study statistician will create schedules which link the gender-specific randomization sequence number, and treatment arm, and the study research nurses will call in all prescriptions thereafter by the randomization sequence number. The independent research pharmacist at the institutional Investigational Drug Service will package drugs/placebos to be similar in appearance effectively keeping all involved masked to treatment assignment.

Statistical analysis plan:

Main Analysis:

All analyses will be conducted separately for men and women based on intention-to-treat. First, we will perform a true multivariate Hotelling t-test to simultaneously compare baseline to 24-month percent change in two primary outcomes (spine and hip BMD) between the arms to protect the type I error rate from outcome multiplicity. If significant, subsequent analyses will be performed without further adjustment for multiplicity. If not, primary outcomes at the primary endpoint will be compared with a conservative Bonferroni correction at $\alpha=0.05/2=0.025$ level. Second, we will fit a series of linear mixed models (SAS® MIXED procedure) with (percent) change from baseline in each of the continuous outcomes as the dependent variable; treatment arm, follow-up time point (6-/12-/18-/24-month or as applicable) and their interaction as the fixed effects of interest; baseline value of the outcome as the sole and a catch-all covariate as an additional fixed effect to preserve the predictability of the primary analytic strategy; and a subject random effect to account for multiple measures from the same patients over time and resulting stochastic non-independence of observations. We will construct contrasts to make between-arm comparisons at each time point. Statistical significance of between arm difference in 24-month change in spine and hip BMD will serve as the formal test of the primary hypothesis. Multiple imputation will be used to handle missing data.