Effects of Denosumab on Bone Mineral Density, Markers of Bone Metabolism and Bone Microarchitecture in Women with Anorexia Nervosa: A Pilot Study

NCT # 03292146

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PARTNERS HUMAN RESEARCH COMMITTEE
PROTOCOL SUMMARY

Answer all questions accurately and completely in order to provide the PHRC with the relevant information to assess the risk-benefit ratio for the study. Do not leave sections blank.

PRINCIPAL/OVERALL INVESTIGATOR
[redacted]

PROTOCOL TITLE
Effects of Denosumab on Bone Mineral Density, Markers of Bone Metabolism and Bone Microarchitecture in Women with Anorexia Nervosa: A Pilot Study

FUNDING
[redacted]

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03.02.2021

SPECIFIC AIMS

Concisely state the objectives of the study and the hypothesis being tested.

This protocol is a randomized, double-blind, placebo-controlled clinical trial which aims to investigate the effect of denosumab on bone mineral density (BMD) in women with anorexia nervosa. We will also investigate the safety of denosumab in women with anorexia nervosa. We hypothesize that 12 months of denosomab administration will result in an increase in bone mineral density, decrease in markers of bone resorption and improvement in bone microarchitecture in osteopenic women with anorexia nervosa compared with placebo.

Specific Aim 1: We hypothesize that 12 months of denosomab administration will result in an increase in bone mineral density in women with anorexia nervosa with low bone mass or osteoporosis compared with placebo.

We will investigate in women with anorexia nervosa in a 12 month study whether treatment with denosumab will increase BMD as measured by dual energy xray absorptiometry (DXA) compared with placebo. The primary endpoint will be lumbar spine BMD at 12 months. Bone density will be measured at baseline, 6 months, and 12 months.

Specific Aim 2: We hypothesize that 12 months of denosomab administration will result in a significant reduction of markers of bone resorption in osteopenic women with anorexia nervosa compared with placebo.

We will investigate in women with anorexia nervosa in a 12 month study whether markers of bone metabolism, including CTx, will decrease in the denosumab group more than in the placebo group. Markers of bone metabolism will be measured at baseline, 1 month, 3 months, 6 months, 7 months, 9 months, and 12 months.

Specific Aim 3: In this exploratory aim, we hypothesize that 12 months of denosomab administration will result in improved bone microarchitecture and strength in osteopenic women with anorexia nervosa compared with placebo.

We will investigate in women with anorexia nervosa in a 12 month study whether treatment with denosumab will improve parameters of bone microarchitecture, as assessed by HR-pQCT, and improve bone strength, as estimated by microfinite element analysis compared with placebo. HRpQCT of the tibia and radius will be performed and the following will be measured: trabecular thickness and spacing; cortical thickness and porosity; ITS (individual trabecula segmentation); finite element analysis modeling of bone strength. HRpQCT will be measured at baseline, 6 months, and 12 months.

Alendronate Extension Study Specific Aims:

Specific Aim 1: Sequential therapy with denosumab followed by a bisphosphonate will increase bone mineral density and decrease bone resorption in women with AN.

We hypothesize that 12 months of denosumab followed by 12 months of open-label alendronate will result in a greater increase in BMD compared to 12 months of placebo followed by 12 months of open-label alendronate.

Specific Aim 2: We hypothesize that within the group of women who receive sequential therapy with 12 months of denosumab followed by 12 months of alendronate, BMD will be maintained between 12 and 24 -months while on alendronate.

We will investigate in a 12-month extension study whether 12 months of open-label treatment with alendronate will maintain the hypothesized gains in BMD achieved after 12 months of denosumab administration.

Specific Aim 3: We hypothesize that within the group of women who receive sequential therapy with 12 months of denosumab followed by 12 months of alendronate, bone microarchitecture and strength will be maintained between 12 and 24 months while on alendronate.

We will investigate in a 12-month extension study whether 12 months of open-label treatment with alendronate will maintain the hypothesized gains in bone microarchitecture, as assessed by HR-pQCT, and bone strength, as estimated by microfinite element analysis, achieved after 12 months of denosumab administration.

BACKGROUND AND SIGNIFICANCE

Provide a brief paragraph summarizing prior experience important for understanding the proposed study and procedures.

Anorexia nervosa (AN) is a serious disease leading to severe bone loss at multiple skeletal sites. The illness affects 1-2% of young women in the U.S. and is chronic in more than 50% of affected women. Bone loss is a severe, frequent and often permanent comorbid medical complication resulting in debilitating vertebral crush fractures. The majority of women with anorexia nervosa have bone loss, and 50% have bone density measurements greater than 2

standard deviations below normative means. It is not uncommon for bone mass in these young women to be comparable to postmenopausal women in their 7th and 8th decades.

Although bone density increases with weight recovery, osteopenia is often a permanent consequence of anorexia nervosa. Significant persistent osteopenia in women with anorexia nervosa has been shown in many studies and both cortical and trabecular bone mineral density (BMD) remain low more than ten years after recovery. Because bone mass remains persistently low despite recovery, such women remain at a high fracture risk throughout life, estimated to be 7.1 times that of healthy women in this age range. These data suggest that there may be a therapeutic window during which effective treatment should be implemented to prevent significant, lifelong bone mass reduction in this vulnerable population.

Adulthood in anorexia nervosa is characterized by a negative balance in bone metabolism, with increased bone resorption and decreased bone formation. This is in contrast to adolescence, which is characterized by a low turnover state – both low bone resorption and formation. A number of therapies targeting the high resorptive state in women with anorexia nervosa have been studied in women with anorexia nervosa, primarily by [redacted]. [redacted] have shown that neither low-dose estrogen at postmenopausal hormone replacement doses or oral contraceptives are effective in women with anorexia nervosa, and bisphosphonates increase bone density significantly but not to normal. Therefore, there is a rationale for antiresorptive therapy in women with anorexia nervosa and data supporting its effectiveness, but a more potent antiresorptive therapy is needed. In addition, as anorexia nervosa is a psychologic illness and such patients are often overwhelmed by the requirements of therapy and the illness itself, a treatment such as denosumab which is administered every 6 months would likely have the benefit of increased compliance and therefore efficacy.

There are no therapies that normalize BMD or that are FDA-approved for bone loss in anorexia nervosa, and in contrast to postmenopausal osteoporosis in which therapy may be life-long, the goal in patients with anorexia nervosa is treatment during the acute illness to reduce further bone loss and fracture risk. We propose that an early relatively short-term intervention with a potent antiresorptive therapy such as denosumab during the period of rapid bone loss may prevent significant osteopenia and reduce fracture risk in women with anorexia nervosa.

We therefore propose a pilot study to determine whether denosumab increases bone density in women with anorexia nervosa. The data generated by this study will provide preliminary data for an application to the NIH for a definitive study to determine whether denosomab is an effective therapy for the treatment of bone loss in women with anorexia nervosa.

Although bone loss in women with anorexia nervosa is severe and may persist after weight normalization, strategies to effectively maximize BMD are lacking. In this proposal, the hypothesis that denosumab administration will improve BMD, bone microarchitecture parameters and bone strength in young women with anorexia nervosa will be tested.

Alendronate Extension Study:

[redacted] recent data provide strong evidence supporting the effectiveness of a bisphosphonate to decrease bone resorption and increase BMD in young women with AN. We hypothesize that bisphosphonates, because of their potent anti-resorptive effects, will consolidate the effects of denosumab to increase BMD in AN. We propose that maximal effectiveness to increase bone

mass in AN will be achieved with sequential therapy with 12 months of denosumab followed by 12 months of alendronate [redacted]. All extension study participants will continue the standard calcium and Vitamin D supplementation for the full 12-month study duration. We propose that this therapy may be effective in reversing bone loss and increasing BMD during a time of active disease.

RESEARCH DESIGN AND METHODS

Briefly describe study design and anticipated enrollment, i.e., number of subjects to be enrolled by researchers study-wide and by Partners researchers. Provide a brief summary of the eligibility criteria (for example, age range, gender, medical condition). Include any local site restrictions, for example, "Enrollment at Partners will be limited to adults although the sponsor's protocol is open to both children and adults."

Subjects: Approximately 75 women will be screened for eligibility in order to identify 30 eligible women with anorexia nervosa, ages 20 to 60, to enroll in the study. Subjects will be randomized in a double-blind fashion to one of 2 groups for 12 months: 1) Denosumab [redacted] at baseline and 6 months or 2) identical placebo injection to determine effects on BMD, markers of bone metabolism, bone microarchitecture, and bone strength at trabecular and cortical sites. All subjects will meet the DSM-V criteria for AN or atypical anorexia and will be assessed for study suitability and monitored throughout the study period for their overall psychiatric clinical state in coordination with the patients' clinical care team by a study psychologist or psychiatric nurse practitioner.

Subject eligibility for the extension study will be based on participation in the main study. Subjects will be given a 6-month supply of alendronate to take home with them at the Month-12 study visit and again at the Month-18 study visit. For subjects who do not live locally or are completing the visit remotely, a 6-month supply of alendronate will be mailed to the subject at the Month 12 and Month 18 study visits. Additionally, subjects will receive medication counseling from a study MD/NP upon initiation of alendronate therapy and will receive the FDA approved alendronate patient medication guide. Treatment compliance with alendronate therapy will be assessed at each study visit by a study MD/NP asking subjects how many tablets have been missed and documenting this on the case report form.

Subjects who were previously enrolled and completed the study when it was a 6-month study of Denosumab or placebo will now have the opportunity to complete months 6 through 12 of the study. For subjects who were participating in the open-label alendronate extension study after completing the 6-month study, they will stop taking the alendronate, complete months 6 through 12 of the main study, and then have the opportunity to take 12 months of open-label alendronate [redacted] after completing months 6 through 12 of the main study.

Inclusion/Exclusion Criteria:

Inclusion Criteria:

- Female
- Age 20-60 years, skeletally mature with closed epiphyses
- Anorexia nervosa or atypical anorexia nervosa defined by DSM-V diagnostic criteria
- BMD T-score < -1.0

- Normal serum 25-OH vitamin D (>30 ng/mL) and calcium levels
- For women of reproductive age, agree to use an effective contraceptive method. Highly effective methods of birth control include:
    - Combined (estrogen and progestogen) hormonal methods (pills, vaginal ring, or skin patch)
    - Intrauterine device (IUD)
    - Intraduterine hormonal-releasing system (IUS)
    - Surgery to tie both fallopian tubes (bilateral tubal ligation/occlusion)
    - Your male partner has had a vasectomy and testing shows there is no sperm in the semen
- Dental check up within the past year

Exclusion Criteria:

- Any disease known to affect bone, including untreated thyroid dysfunction, Cushing's or renal failure
- Any medication known to affect bone metabolism within 3 months of the study, excluding oral contraceptives or other forms of estrogen administration. Bisphosphonates must have been discontinued for at least one year before participation
- Immunodeficiency or taking immunosuppressive therapy
- Serum potassium <3.0 meq/L
- Serum ALT >3 times upper limit of normal
- eGFR of less than 30 ml/min
- Hypocalcemia
- Diabetes mellitus
- Active substance abuse, including alcohol
- History of malignancy
- Paget disease of bone
- Osteomalacia
- Osteonecrosis of the jaw (ONJ) or risk factor for ONJ, such as invasive dental procedures (eg, tooth extraction, dental implants, oral surgery in the past 6 months), poor oral hygiene, periodontal and/or pre-existing dental disease, and current use of corticosteroids.
- Planned invasive dental procedure over the next 24 months.
- Known senstivity to any of the products or components to be administered during dosing or known sensitivity to mammalian cell derived drug products
- Sensitivity to calcium or vitamin D supplements
- Pregnant, planning to become pregnant with 7 months after the end of treatment and/or breastfeeding

Alendronate Extension Exclusion Criteria:

Exclusion Criteria:

- Subjects with a known esophageal disease
- Abnormalities of the esophagus such as stricture or achalasia
- Inability to sit/stand upright for at least 30 minutes
- Hypersensitivity to any component of alendronate

Briefly describe study procedures. Include any local site restrictions, for example, "Subjects enrolled at Partners will not participate in the pharmacokinetic portion of the study." Describe study endpoints.

Screening Visit: A "Screening Visit" will be conducted by a member of the study clinical team to determine eligibility for the protocol. All subjects will be seen [redacted] for an outpatient visit including the following: A complete medical history, physical examination and urine pregnancy test. History taking will include complete eating disorder, weight, menstrual, and medication histories. In addition, the following will be performed:

1. Blood draw for comprehensive metabolic panel, cbc, and 25 OH Vitamin D
2. Nutritional evaluation, including weight in a gown, height, frame size, calculation of percent IBW and body mass index (BMI)
3. DXA scan of the spine, hip, radius, and total body is required if the subject has not had a DXA scan within 6 months prior to the screening visit and optional if she has
4. Determination of anorexia nervosa diagnosis and subtype (restricting or binge/purge) using DSM-V criteria
5. Verification of the anorexia nervosa diagnosis
6. Verification of lack of severe comorbid concerns (i.e. suicidality, substance use) that would preclude safe study participation will occur by the study psychologist or psychiatric nurse practitioner. Suicidality is assessed through a verbal conversation with a psychiatric health professional. If the subject has been suicidal in the past, the psychiatric professional will ask questions to assess their level of suicidality, and whether it would be a risk to their health to partake in a study. If a subject appears to be actively suicidal, study staff will make appropriate referrals, which will often include the [redacted]; all efforts will be made to contact the subject's clinical treatment team.
7. Plain film of wrist/hand to determine bone age in women with primary amenorrhea who have not received estrogen for ≥1 year.

Baseline Visit: Eligible study subjects (n=30 women with anorexia nervosa or atypical anorexia) will be assessed at an outpatient visit [redacted] for baseline testing.

1. A complete medical history including menstrual history and instructions on keeping a menstrual diary, consumptive habits (smoking, alcohol, caffeinated beverages) will be recorded, oral temperature, height and weight in gown, pulse and blood pressure, and physical examination will be performed
2. Urine pregnancy test
3. DXA scan of the spine, hip, radius, and total body if screen visit did not take place within 1 month of baseline visit or if a DXA scan was not performed at the screening visit.
4. Baseline hormone and safety blood testing
5. HR-pQCT and FEA of the radius and tibia on two machines as we are transitioning the study from the XCT1 machine to the XCT2 machine because the XCT1 machine is being taken out of service
6. Subjects will take a standard dose of [redacted] calcium and [redacted] Vitamin D supplements daily throughout the study.
7. Eating Disorder Examination—Questionnaire
8. Eating Disorder Inventory-2
9. Paffenbarger Exercise Questionnaire

10. Calcium and vitamin D food frequency questionnaire

Randomization to treatment or placebo group will occur at the baseline visit. Twenty subjects will be randomized to active denosumab [redacted] and 10 subjects will be randomized to an identical placebo injection. Randomization will be stratified for presence or absence of atypical anorexia nervosa, defined as Body Mass Index (BMI) ≥ 18.5 kg/m^2 vs. < 18.5 kg/m^2. A second injection of active denosumab [redacted] or an indentical placebo injection will be given at the month 6 visit.

After the baseline visit, follow-up blood testing for electrolytes, including calcium, and a CBC, will occur at 10 days, 1 month, 3 months, 6 months, 6 months and 10 days, 7 months, 9 months and 12 months after baseline testing. A pregnancy test and clinical evaluation will be performed at the 1, 3, 6, 7, 9 and 12-month visits, as will a nutrition evaluation, including weight in a gown, height, and calculation of percent IBW and body mass index (BMI) and completion of questionnaires (calcium and vitamin D food frequency questionnaire and Paffenbarger exercise questionnaire). BMD at the spine, hip, radius and total body will be performed 6 and 12 months after baseline. HR-pQCT and FEA of the radius and tibia will be performed at 6 and 12 months after baseline. Markers of bone metabolism will be measured at months 1, 3, 6, 7, 9 and 12 months. A 25 OH Vitamin D will be assessed at the 12-month study visit.

Alendronate Extension Study:
Subjects with a known esophageal disease cannot participate in the alendronate extension study. Subjects who enroll in the extension study will return for two additional study visits at 18 and 24 months. A clinical evaluation and pregnancy test will be performed at both visits, as will a nutrition evaluation, including weight in a gown, height, and calculation of percent IBW and body mass index (BMI) and completion of questionnaires (calcium and vitamin D food frequency questionnaire at 24 Months and Paffenbarger exercise questionnaire at 18 Months and 24 Months). BMD at the spine, hip, radius and total body and HR-pQCT and FEA of the radius and tibia will be performed at the 24 month study visit. The HR-pQCT and FEA of the radius and tibia will be performed on two scanners because the study is transitioning from one scanner to another.

Subjects who do not live locally will be permitted to have their blood drawn and pregnancy test performed offsite for lab tests required for the visit. Subjects who choose this option will also have an interim history performed by our staff by telephone. For visits which involve questionnaires, those will be mailed or sent electronically to the subject to be completed and returned to study staff. Tests that need to be run in real time will be done at local laboratories, with the results provided online to investigators. Otherwise, the samples will be mailed to investigators.

Study Visit	Screen	Baseline	Day 10	M1	M3	M6	Day 10	M7	M9	M12	M18	M24
Consent	X									X		
Clinical assessment and HCG	X	X		X	X	X		X	X	X	X	X
Safety Labs (comprehensive metabolic panel including calcium, CBC)	X	X	X	X	X	X	X	X	X	X		
Nutrition Evaluation (height, weight)	X	X		X	X	X		X	X	X	X	X

Bone Markers (CTX, P1NP, osteocalcin)		X		X	X	X		X	X	X	X	X
IGF-1, estradiol, SHBG, testosterone		X				X				X		
25 OH VitD	X									X		
BMD (DXA)	X	X				X				X		X
Bone Strength with FEA (Xtreme CT)		X				X				X		X
EDI-2		X			X	X			X	X	X	X
EDE-Q		X			X	X			X	X	X	X
Paffenbarger Questionnaire (exercise quantification)		X				X				X	X	X
Calcium and Vitamin D Food Frequency Questionnaire		X				X				X		X

For studies involving treatment or diagnosis, provide information about standard of care at Partners (e.g., BWH, MGH) and indicate how the study procedures differ from standard care. Provide information on available alternative treatments, procedures, or methods of diagnosis.

No treatment thus far has been successful in increasing bone density in women with anorexia nervosa. Weight gain is associated with some increase in bone density, but is difficult to attain (occurs in only 50%) and sustain. The DXA scan is the best validated method currently used clinically to assess bone mass and fracture risk. This is the standard method of diagnosis [redacted], and is provided for free to study subjects. There are currently no FDA-approved therapies for anorexia nervosa-induced bone loss.

Alternate strategies to address low bone density in AN
Recovery of weight and menses: Although weight and menses recovery is associated with some increase in BMD, this increase is not sufficient to cause bone accrual to normalize, and BMD remains lower than in controls. Additionally, recovery can be hard to attain and sustain.

Calcium and vitamin D supplementation: Many studies have now shown that calcium and vitamin D supplementation is not sufficient to increase BMD in AN. BMD remains low in these women despite higher calcium and vitamin D intake than in controls

Alternate strategies to assess bone microarchitecture and strength: MRI of the peripheral skeleton has lower resolution, longer scan time and increased susceptibility to image post-processing.

Describe how risks to subjects are minimized, for example, by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk or by using procedures already being performed on the subject for diagnostic or treatment purposes.

The intervention being provided involves no more than two subcutaneous injections for a period of 12 months. For subjects enrolling in the alendronate substudy, they will be taking a tablet [redacted] for 12 months from month 12 to month 24. A number of procedures will be instituted to protect against potential risk involved in this protocol. All subjects will have pregnancy tests at the screening visit and at the baseline visit, prior to any radiologic procedures and prior to receiving any study medication. Subjects will be instructed on the importance of contraception

during the course of the study and will also have pregnancy tests at each study visit. Any subject who becomes pregnant during the course of the study and is discharged from participation will undergo a follow-up study visit. This will include assessment by an MD or NP for study medication related side effects, including hypocalcemia, and measurement of a calcium level if it has not been done clinically. Patients will be carefully monitored by clinicians for side effects and potential toxicities.

All unanticipated problems, including adverse events will be reported [redacted] as required.

Describe explicitly the methods for ensuring the safety of subjects. Provide objective criteria for removing a subject from the study, for example, objective criteria for worsening disease/lack of improvement and/or unacceptable adverse events. The inclusion of objective drop criteria is especially important in studies designed with placebo control groups.

Subjects will be instructed to call us if they develop any potantial side-effects. Subsequent management will be decided based on the severity of the side-effect.

Serious side effects related to study drug will necessitate protocol discontinuation. If a subject develops a minor side effect, she will be asked to continue as per the protocol. To minimize the risk from radiation, scans will not be performed on subjects until a negative pregnancy test result is obtained. If lab abnormalities are discovered, the subject and their physician, if authorized by the subject, will be notified.

If subjects are uncomfortable with any portion of any study visit, this portion will be discontinued or not performed.

Drop criteria for subjects:

1. Pregnancy (for any subject)
- If a subject has an invasive dental procedure (eg, tooth extraction, dental implants, oral surgery) during the study their participation in the study may be paused or discontinued after consultation with their dentist or oral surgeon.
2. Medical instability, which will be determined by the study physician. Patients in this category will be assessed by the DSMB, and continue to be assessed according to study protocol
3. Serious study–related adverse event

FORESEEABLE RISKS AND DISCOMFORTS

Provide a brief description of any foreseeable risks and discomforts to subjects. Include those related to drugs/devices/procedures being studied and/or administered/performed solely for research purposes. In addition, include psychosocial risks, and risks related to privacy and confidentiality. When applicable, describe risks to a developing fetus or nursing infant.

Blood Sampling:
There is a risk of superficial bruising and discomfort at the venepuncture site. Rarely, fainting (from a vasovagal episode) or a treatable infection may occur.

In concordance with the IRB guidelines, the total amount of blood drawn will not exceed 550 cc over an eight-week period for study subjects whose weights are above 75% of ideal body weight and at least 110 pounds.

Radiation:
The main research study involves exposure to radiation from four or five DXA scans and three HR-pQCT scans. The total radiation dose the subject will receive from all of the scans is 0.225 milliSievert (mSv). This amount of radiation is approximately 7 % of the yearly natural background radiation from the earth and the sky (equivalent to 26 days of background radiation). There are no known health risks associated with such a dose.

Subjects will have the option to repeat scans once if there is a technical issue with the machine, which is a rare occurrence. If each scan was repeated twice at each visit, this would add no more than 0.045 mSv of radiation exposure, making the total radiation dose the subject would receive from all of the scans no more than 0.27 mSv. This amount of radiation is equal to about 9% of the annual background radiation from the earth and the sky (equivalent to 31 days of background radiation). Subjects have the option to refuse to be re-scanned.

The alendronate substudy involves exposure to radiation from one additional set of DXA scans and two HR-pQCT scans. The total radiation dose the subject will receive from these additional scans is 0.04 milliSievert (mSv). This amount of radiation is approximately 1% of the yearly natural background radiation from the earth and the sky (equivalent to 5 days of background radiation).

All patients will have pregnancy tests on admission prior to receiving any radiation. Subjects will also have serial pregnancy tests performed at every study visit. BMD measurements will occur at four times (5 times if subject is participating in the extension study), and HR-pQCT of the radius and tibia will be performed four times over the course of 24 months.

Complications of medications:
Denosumab is administered as a single subcutaneous injection once every 6 months. Denosumab is approved by the FDA to treat osteoporosis in women after menopause that are at high risk for fracture. Denosumab has been used successfully in the treatment of postmenopausal women with osteoporosis at high risk for fracture with few side effects. Since it was first approved for sale in May 2010, approximately 11.8 million people have been prescribed denosumab. Taking denosumab [redacted] may cause all, some or none of the side effects listed.

Very Common side effects (which may affect more than 1 person in 10):

- Transient (going away quickly) mild irritation or tenderness at the injection site.
- Joint pain
- Pain in extremity

Common side effects (which may affect between 1 and 10 people in every 100):

- Cataracts
- Cough
- Decreased skin sensation
- Dizziness

- Difficulty emptying the bladder
- Eczema
- Low blood calcium levels (especially if you have kidney problems)
- Muscle and bone pain
- Osteoarthritis
- High cholesterol
- Hair loss (alopecia)

Uncommon side effects (which may affect between 1 and 10 people in every 1,000):

- Skin infections
- Broken bones in your spine after stopping denosumab
- Rash that may occur on the skin or sores in the mouth

Rare side effects (which may affect 1 and 10 people in every 10,000):

- Allergic reaction: hives, rash, headache, difficulty breathing; swelling of your face, lips, tongue, or throat, nausea and sometimes vomiting
- Allergic reaction that can damage blood vessels mainly in the skin (e.g., purple or brownish-red spots, hives or skin sores) (hypersensitivity vasculitis)
- Osteonecrosis of the jaw (breakdown and non healing of jaw tissue)
- Unusual thigh bone fractures (atypical femoral fractures)

Side effect of unknown prevalence:

- Severe allergic reaction with skin eruptions/blisters, fever and increased eosinophil counts (a type of white blood cell) with possible organ damage (drug rash with eosinophilia and systemic symptoms)

The potential effects of denosumab on the fetus are not known, and therefore precautions against administration to pregnant patients will be instituted. All patients will have pregnancy tests on admission prior to receiving study medication and serial pregnancy tests at every study visit and will be required to use contraception in order to participate in the protocol.

Hypocalcemia may be exacerbated by the use of Denosumab. All potential subjects will have their calcium level tested at the screening study visit. Any pre-existing hypocalcemia will be reported to the subject and their clinical care team and corrected prior to initiating therapy with Denosumab. Additionally, all subjects will be adequately supplemented with [redacted] calcium and [redacted] Vitamin D throughout study participation. These supplements are required for study participation.

After patients start taking densoumab [redacted], it is possible that their body may make antibodies or may cause side effects. The development of antibodies to densoumab in patients has been uncommon and has had no clinical effects and has not reduced the effect of densoumab on bones.

The potential risk of alendronate in this study is not greater than that associated with its common use in clinical practice. These risks include abdominal or stomach pain, skin rash, diarrhea, headache and joint pain. Less common side effects include severe abdominal pain or stomach pain, stomach cramping, belching, bone pain, blurred vision or change in vision, chest pain,

constipation, cough, dizziness, dry eyes, fever, general feeling of discomfort or fullness, leg cramps, nausea, ringing in the ears, swelling of feet or lower legs, and weakness. On rare occasion, red sore eyes have been reported. Although the long-term risk of alendronate in young women is unknown, bisphosphonates have been used in premenopausal women to treat osteopenia due to glucocorticoids. In addition, these medications are used widely in the community and it is essential that their efficacy be assessed. Bisphosphonates remain in the bones for many years after administration, and it is unknown whether bisphosphonates may be secreted from bone during pregnancy or breastfeeding.

There may be other risks of denosumab and alendronate that are currently unknown.

Oral calcium can cause constipation and a metallic taste in the mouth.
Vitamin D in the doses being administered does not cause any side effects.

EXPECTED BENEFITS

Describe both the expected benefits to individual subjects participating in the research and the importance of the knowledge that may reasonably be expected to result from the study. Provide a brief, realistic summary of potential benefits to subjects, for example, "It is hoped that the treatment will result in a partial reduction in tumor size in at least 25% of the enrolled subjects." Indicate how the results of the study will benefit future patients with the disease/condition being studied and/or society, e.g., through increased knowledge of human physiology or behavior, improved safety, or technological advances.

[redacted]

[redacted]

EQUITABLE SELECTION OF SUBJECTS

The risks and benefits of the research must be fairly distributed among the populations that stand to benefit from it. No group of persons, for example, men, women, pregnant women, children, and minorities, should be categorically excluded from the research without a good scientific or ethical reason to do so. Please provide the basis for concluding that the study population is representative of the population that stands to potentially benefit from this research.

[redacted]

When people who do not speak English are excluded from participation in the research, provide the scientific rationale for doing so. Individuals who do not speak English should not be denied participation in research simply because it is inconvenient to translate the consent form in different languages and to have an interpreter present.