DENOSUMAB IN ADDITION TO INTENSE URATE-LOWERING THERAPY FOR BONE EROSIONS IN GOUT: A PILOT STUDY

Clinical Trials Identifier: NCT02903446

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1 Contents

2 Summary

Title: Denosumab in Addition to Intense Urate-Lowering Therapy for Bone Erosions in Chronic Tophaceous Gout
Duration: 3 years
Study Site(s): New Zealand - University of Auckland, USA- University of Alabama at Birmingham
Approximate number of participants: 20
Investigators: Angelo L. Gaffo MD, Nicola Dalbeth MD, Kenneth G. Saag MD, MSc.
Methodology: Open label Randomized multicenter pilot trial to evaluate if the addition of Denosumab to intense urate-lowering therapy will lead to a reduction in computerized tomography (CT) erosion scores in patients with radiographic damage caused by gout or chronic tophaceous gout. Protocol – Denosumab and Urate-Lowering Therapy

List Abbreviations, Tables, and Figures

Abbreviations :

ACR	American College of Rheumatology
AE	Adverse Event
BMD	Bone Mineral Density
CBC	Complete Blood Count
CC	Coordinating Center
CFR	Code of Federal Regulation
CITI	Collaborative Institutional Training Initiative
CMP	Complete Metabolic Profile
CT	Computerized Tomography
CTX	Serum C-Terminal Telopeptide
DHHS	Department of Health and Human Services
EULAR	European League Against Rheumatism
FDA	Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
HAQ-II	Health Assessment Questionnaire-II
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus
HCG	Human chorionic gonadotropin
IC	Informed Consent
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
IT	Information Technology
MT	Metatarsal
OHRP	Office of Human Research Protections
OPG	Osteoprotegerin
OP	Osteoporosis
ONJ	Osteonecrosis of the Jaw
PHI	Personal Health Information
PI	Principal Investigator
PII	Personally Identifiable Information
PMC	PubMed Central
PFS	Pre-Filled Syringe
QA/QC	Quality Assurance/Quality Control
QOL	Quality of Life
OHRP	Office of Human Research Protections
RANKL	Receptor Activator Of Nuclear Factor Kappa-B Ligand

RBC	Red Blood Cells
RCT	Randomized Clinical Trial
SAS	Statistical Analysis System
SAP	Statistical Analysis Plan
SC	Subcutaneous
SD	Standard Deviation
SOP	Standard Operating Procedure
SAE	Serious Adverse Event
SUSARs	Suspected Unexpected Serious Adverse Reaction
sUA	Serum Uric Acid
ULA	Urate-lowering Agent
ULT	Urate-lowering Therapy
UAB	University of Alabama at Birmingham
VAS	Visual Analog Scale

3 Background

Bone erosions are a common manifestation and cardinal feature of structural damage in chronic tophaceous gout. Management of this destructive and often debilitating gout complication has focused exclusively on urate-lowering therapy (ULT) but little attention has been given to prevention or reversal of gouty erosions and other structural damage caused by gout.[1,2] A recently published clinical trial with zoledronic acid failed to show an effect in bone erosions among individuals with chronic tophaceous gout, despite improvements in bone mineral density (BMD) and bone turnover markers.[3] However, it is known that increased numbers of osteoclasts in patients with tophaceous gout are most likely a result of enhanced osteoclastogenesis as these patients also have higher circulating levels of receptor activator of nuclear factor kappa-B ligand (RANKL). Furthermore, peripheral blood mononuclear cells and synovial fluid mononuclear cells taken from patients with erosive gout preferentially formed osteoclast-like cells in the presence of RANKL. The number of osteoclasts formed significantly correlates with the number of tophi in gout patients. [4]

Denosumab (Prolia®) is a fully human monoclonal antibody with a high affinity (Kd 3 x 10(-12)M) for RANKL that can bind and neutralize the activity of human RANKL similar to the action of endogenous osteoprotegerin (OPG). Given the relevance of RANKL in the mechanism of gouty erosions,[4] a central hypothesis of this pilot study is that denosumab is more likely to precisely target the mechanism of gouty erosions relative to zoledronic acid.

4 Rationale for the Study

Since there is no known effective treatment to attenuate or improve structural damage caused by gout, and an appreciable effect is not evident with zoledronic acid, we propose a pilot, controlled, proof-of-concept study in which denosumab will be added to standard ULT in 20 patients with erosive gout.

Erosive gout can be a debilitating and deforming arthritis with a profound impact on quality of life (QOL) and patient's productivity. Although many of these effects can be traced to flares and chronic pain, deformities induced by tophi are known to compromise joint and limb function. Slowing or reversing erosions induced by gout has potential to impact both the patient's QOL and ability to function.

The rationale for using denosumab is that we hypothesize the addition of this drug to standard ULT will improve structural damage caused by gout through targeting a known mechanism of the gouty erosive process (inhibition of RANKL).

5 Research Strategy

5.1 Study Design

This is an open-label, randomized, parallel-group pilot clinical trial in which 20 participants with at least one confirmed conventional radiographic foot bone erosion will be assigned in a 1:1 allocation to one the following groups:

- Denosumab 60 mg administered subcutaneously (SC) every 6 months for a year + ULT standard of care

OR

- ULT standard of care

All subjects will continue on ULT standard of care and will need to have a serum urate level of ≤5 mg/dL (300 µmol/L) at the time of randomization. Patients will continue prescribed ULT throughout the study. Gout flares will be treated as per local practice guidelines. The study design is shown in figure 1.

5.2 Rationale for Study Design

- **Open-label design**: The pilot nature of this study will not allow for a double-blind design, but given that the primary outcome is radiographic (which will be interpreted blinded to exposure category) this is unlikely to introduce significant bias.
- **Need for active comparator:** Prior studies have demonstrated that ULT is important to achieve a successful radiographic outcome in gout. In addition, standard of care practice requires patients to be on ULT, which is appropriate for a comparator arm. The natural history of gouty erosions will not be able to be ascertained for comparison without a comparator arm group.
- **Study duration**: 12 months of follow-up will be sufficient for the sensitive computerized tomography (CT) scan erosion outcome.

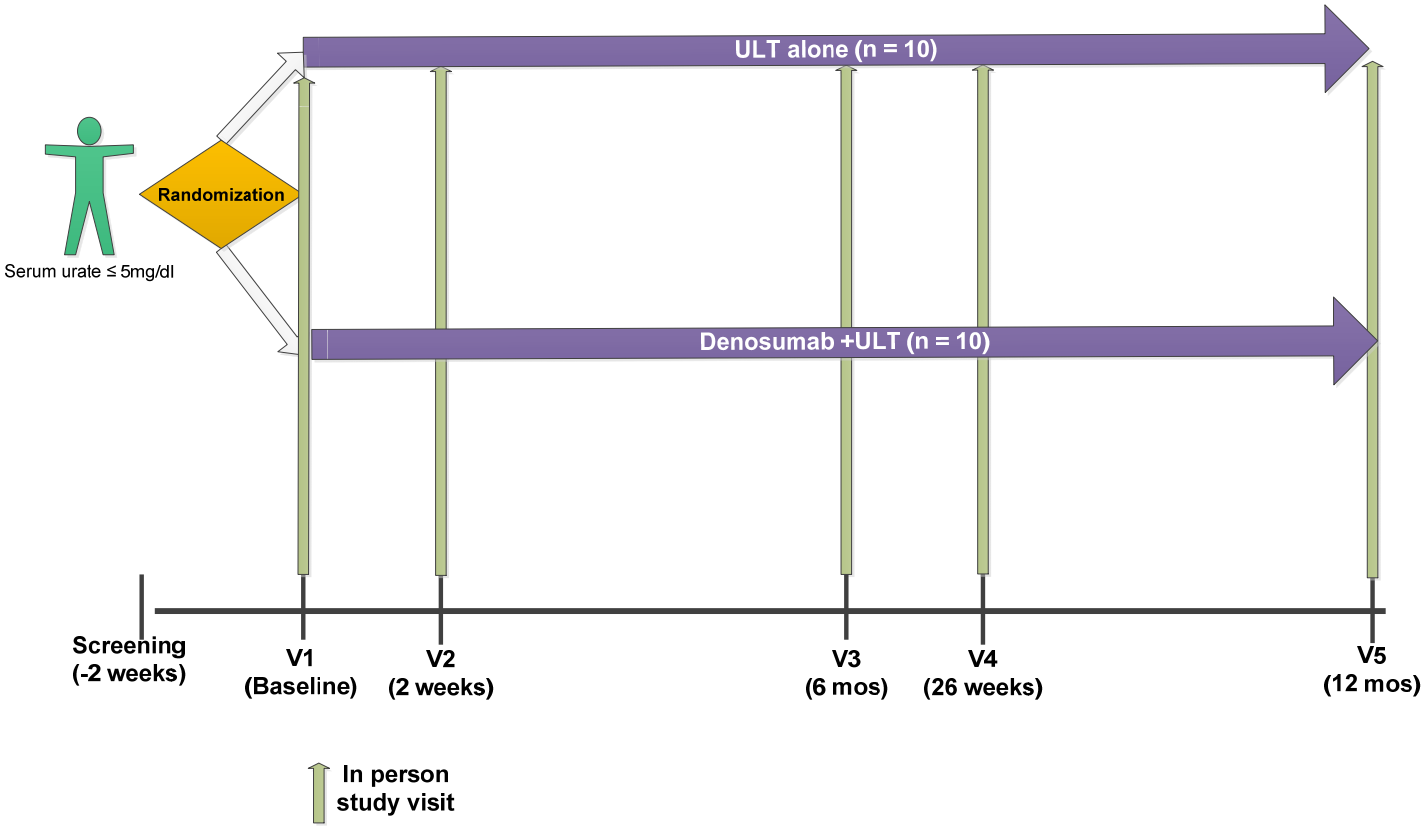
6 Outcomes

6.1 Primary Outcome

The primary outcome in this pilot study will be change in the foot computed tomography (CT) bone erosion score from baseline to 12 months. CT images of both feet will be obtained at the beginning of the study and at the 12 month visit. While plain film radiography remains the standard imaging technique we have chosen CT, since it is a more sensitive imaging technique to evaluate changes in bone erosions. [5] [6] [7] In addition, CT can be used to study the effects of gout in areas that are hard to visualize with plain film radiography. The participants will be positioned feet first in a supine position with the feet in a plantar flexion position. Ankles and feet will be scanned axially in one helical acquisition. CT bone erosion volume in both feet will be scored using a CT bone erosion scoring method, based on the Rheumatoid Arthritis MRI score (RAMRIS) for erosion, as previously validated. [8] [9] This same system was successfully used in our prior study of improvement of gout

erosions with zoledronic acid. [3] The gout CT bone erosion scoring system includes the following bones for erosion on a semi quantitative scale from 0 to 10 in each foot: 1st metatarsal (MT) head, 2nd – 4th MT base, cuboid, middle cuneiform, distal tibia (maximum total score 140). All CT scans will be scored at the end of the study (paired scans from baseline and year 1 with order known) by a single musculoskeletal radiologist with experience in this technique and who is blinded to treatment allocation.[3]

Figure1: Study Design



6.2 Secondary Outcomes

- Decrease in bone reabsorption as measured by serum CTX levels over 12 months
- Subject reported functional status (disability) by Health Assessment Questionnaire-II (HAQ-II) will be assessed from baseline over 12 months
- Subject reported change in physical and mental health by Short Form Health Survey (SF-12) scores assessed from baseline over 12 months
- Assessment of pain score by visual analogue scale (VAS) reported from baseline over 12 months

7 Patient Population

7.1 Inclusion Criteria

- Age 30 years or older and able to provide informed consent
- Diagnosis of gout according to the American College of Rheumatology (ACR) / European League Against Rheumatism (EULAR) classification criteria
- Radiographic foot bone erosion attributable to gout and confirmed by a radiologist or any previous x-ray in the past two years showing erosions

- Serum urate of ≤ 5 mg/dL (300 µmol/L) * on current urate oral lowering therapy (allopurinol, probenicid, febuxostat, benzbromorone)

7.2 Exclusion Criteria

- Treatment with bisphosphonates in the preceding 2 years
- Any prior treatment with denosumab (PROLIA) in the past 2 years
- Women of childbearing potential, who are not currently using birth control, are pregnant, planning to become pregnant, or are breast-feeding
- Men planning to conceive in the next 12 months
- Unstable systemic medical condition
- Uncontrolled hyperthyroidism
- Uncontrolled hypothyroidism
- History of Addison disease
- History of osteomalacia
- History of osteonecrosis of the jaw (ONJ)
- History of atypical femur fracture
- History of tooth extraction, jaw surgery, dental implants, or other dental surgery within the prior 6 months
- History of anorexia nervosa, bulimia (by history or physical) or obvious malnutrition.
- Invasive dental work(implants/surgery) planned in the next 2 years
- History of Paget's disease of bone
- Other bone diseases which affect bone metabolism
- Vitamin D deficiency [25(OH) vitamin D level < 20 ng/mL (<49.9 nmol/L)]†
- Hypercalcemia
- Elevated transaminases ≥ 2.0 x upper limit of normal (ULN)
- Elevated total bilirubin > 1.5x ULN
- History of any solid organ or bone marrow transplant
- Malignancy within the last 5 years (except cervical carcinoma *in situ* or basal cell carcinoma)
- Hypocalcemia
- Estimated glomerular filtration rate < 30 mL/minute/1.73 m^2
- Current use of any biological therapy (eg. infliximab, etanercept, adalimumab, etc.)
- Treatment history with pegloticase or another recombinant uricase within 6 months prior to randomization.
- Recipient of an investigational drug within 4 weeks prior to study drug administration or plans to take an investigational agent during the study

*Potential participants could be re-screened after a periord on urate-lowering therapy prescribed by their primary care physician/health care provider;
† Potential participants could be re-screened after a periord of vitamin D supplementation as prescribed by their primary care physician/health care provider.

8 Study Procedures and Assessments

All study visits and procedures will be performed in facilities in the University of Alabama at Birmingham (UAB), USA and University of Auckland, New Zealand

8.1 Screening Visit

At the screening visit, the study objectives will be explained to potential participants. Participants will have the opportunity to ask questions before any protocol-specified screening procedures are initiated and informed consent (IC) is obtained. After consent is obtained, a study ID will be assigned. During the screening visit, the following procedures will be performed, and information will be obtained to determine eligibility to continue in this research study. A copy of the signed and dated informed consent form (ICF) will be provided to the patient.

The following procedures will be completed during the screening visit:

- Review inclusion/exclusion criteria

- IC
- Date of birth
- Self-reported race/ethnicity
- Focused medical history
- Medical conditions that might preclude study participation
- Assess gout history and symptom severity
- Medication review
    - Medication history (including use of: over the counter medications (eg. aspirin), other prescription medications (eg. gout medications))
    - Dietary supplement/vitamin use
- Physical exam includes, but is not limited to
    - Dermatological
    - Chest and cardiac
    - Abdominal
    - Musculoskeletal and nervous system examinations
    - Weight/Height
- Screening visit laboratory
    - Complete blood count (CBC) with differential
    - Comprehensive metabolic panel (CMP)
    - Serum urate level (sUA)
    - Serum pregnancy test in non-postmenopausal women‡
    - Vitamin D
    - Intact PTH
- Review of ULT and gout flare prophylaxis

‡Defined as a woman: Age ≥ 55 years, with cessation of menses for 12 or more months; Age < 55 years, but no spontaneous menses for at least 2 years; Age < 55 years and spontaneous menses within the past 1 year, but currently amenorrheic (eg, spontaneous or secondary to hysterectomy), AND with documented postmenopausal gonadotropin levels (luteinizing hormone and follicle-stimulating hormone levels > 40 IU/L) or postmenopausal estradiol levels (< 5 ng/dL) or according to the definition of "postmenopausal range" for the laboratory involved; Underwent a bilateral oophorectomy.

8.2 Visit 1 (Baseline-Day 0)

Baseline, Visit 1 will occur within 2 weeks of the screening visit and signing of the ICF, and at a time when the participant is not having a gout flare or is felt to be at their baseline status of chronic tophaceous gout. Before this visit, investigators will contact participants to confirm that they are not actively having a gout flare according to standard definition. [2] [10] If the participant is having a gout flare in the 24-48 hours before the scheduled visit, the visit will be postponed for a week. Denosumab will not be administered to participants who are actively having a gout flare. During the baseline visit the markers for the study primary and secondary outcomes will be assessed as well as additional data collection needed for safety monitoring.

- Obtain and record vital signs, including pulse rate, sitting blood pressure, and body temperature
- Laboratory
    - Blood draw
        - CMP
        - Bone Turnover (serum CTX)
        - Serum banking
    - Urine collection
        - Pregnancy test
- CT scan of the feet (link to section)
- Gout therapeutics assessment: review of ULTs and use of medications for gout flare prophylaxis and gout flares
- Review concomitant medications
- Physical exam includes, but is not limited to
    - Dermatological
    - Chest and cardiac
    - Abdominal

    - Musculoskeletal and nervous system examinations
    - Weight/Height
- Assessment of functional status (disability) by Health Assessment Questionnaire-II (HAQ-II), physical and mental health by SF-12 scores, and pain score by visual analogue scale (VAS)
- Administer denosumab in patients randomized to this treatment arm

Participants will be advised to maintain adequate calcium and vitamin D intake per USDA and DHHS guidelines.

8.3 Visit 2 (2-4 weeks)

Participants will report 2- 4 weeks following administration of denosumab (Visit 1) to check serum calcium levels

- Laboratory
    - Blood draw
        - Calcium

8.4 Visit 3 (6-7 months)

Similar to visit 1, participants will be contacted to make sure that they are not having a gout flare in the 24-48 hours prior to the scheduled visit.

- Physical exam includes, but is not limited to
    - Dermatological
    - Chest and cardiac
    - Abdominal
    - Musculoskeletal and nervous system examinations
    - Weight/Height
- Obtain and record vital signs, including pulse rate, sitting blood pressure, and body temperature
- Laboratory
    - Blood Draw
        - CBC with differential
        - CMP
        - Bone Turnover (serum CTX)
        - sUA
        - Serum banking
    - Urine collection
        - Pregnancy test
- Assess AEs
- Review concomitant medications
- Gout therapeutics assessment: review of ULTs and use of medications for gout flare prophylaxis and gout flares
- Assessment of functional status (disability) by HAQ-II, physical and mental health by SF-12 scores, and pain score by VAS
- Administer denosumab in patients randomized to this treatment arm

Participants will be advised to maintain adequate calcium and vitamin D intake per USDA/DHHS and Ministry of Health guidelines.

8.5 Visit 4 (26-28 weeks)

Participants will report 2 weeks following denosumab (Visit 3) to check serum calcium levels

- Laboratory
    - Blood draw
        - Calcium

8.6 Visit 5 (12 months / Final visit)

The following procedures will be completed:

- Obtain and record vital signs, including pulse rate, sitting blood pressure, and body temperature.
- Laboratory
    - Blood Draw
        - CBC with differential
        - CMP
        - sUA
        - Serum banking
        - Bone Turnover (serum CTX)
- Assess AEs
- CT scan of the feet
- Gout therapeutics assessment: review of ULTSs and use of medications for gout flare prophylaxis and gout flares
- Review concomitant medications
- Physical exam includes, but is not limited to
    - Dermatological
    - Chest and cardiac
    - Abdominal
    - Musculoskeletal and nervous system examinations
    - Weight/Height
- Assessment of functional status (disability) by HAQ-II, physical and mental health by SF-12 scores, and pain score by VAS
- Review end of study procedures with the participant

Table1. Schedule of visits and evaluations

	Screening	V1 Baseline	V2	V3	V4	V5 Final
Months (weeks)	-2 Week	0	(2 -4 Weeks)	6-7 Months	(26-28 Weeks)	12
Visit description / Study procedures						
Informed consent	X					
Inclusion/exclusion criteria	X					
Focused medical history and physical examination	X	X		X		X
Vital signs*	X	X		X		X
Pregnancy test §	X (serum)	X (urine)		X(urine)		
Laboratory						
Blood draw		X	X		X	
CBC with diff	X			X		X
CMP	X	X		X		X
Calcium			X		X	
Serum urate	X			X		X
Vitamin D	X					
Intact PTH	X					
Bone Turnover (serum CTX)/Biomarker Banking		X		X		X
Urine Collection		X		X		
CT scan of feet		X				X
Administer denosumab[+]		X		X		
Assess AEs and gout flares		X		X		X
Review concomitant medications	X	X		X		X

Assessment of functional status (disability) by HAQ-II ,physical and mental health by SF-12 scores , and pain score by VAS reported		X		X		X

CMP = Complete metabolic profile, CBC with diff = Complete blood count with Differentiation, HAQ-II = Health Assessment Questionnaire-II, VAS = Visual Analog Scale , * Includes sitting blood pressure, heart rate, respiratory rate, and body temperature; + For patients randomized to denosumab, § Serum human chorionic gonadotropin (hCG) assessment for premenopausal women will be done at screening visit with urine stick thereafter before each denosumab dose

9 CT scan of feet:

CT images of both feet will be obtained at the beginning and the end of the study (V1 and V5). The participants will be positioned supine with the knees bent at 90 and the feet dorsiflexed 45. Both feet will be scanned together with the CT gantry vertical. The range covered was from 5 cm above the ankle joint to the ends of the toes. All scans will be performed with the same image protocol of acquisition at 16 x 0.75 mm, reconstructed on a bone algorithm, 768 matrix, to 0.8 mm slices with a 0.4 mm increment (kVp 140, 120 mAs/slice). Additional reconstructions will be done on a soft tissue algorithm, 512 matrix, also to a 0.8 mm slice with a 0.4 mm increment. Images will be transferred via encrypted UAB Sharefile portal or via encrypted hard disc shipped via courier to the University of Auckland to be read. .

The CT scans will be analyzed for bone erosions by a trained musculoskeletal radiologists (Anthony Doyle) who will be blinded to the clinical details or plain radiographic damage scores. Bone erosion will be assessed using reformatted images in the anatomical, axial, sagittal and coronal planes. Erosions on CT are defined as focal areas of loss of cortex with sharply defined margins, seen in two planes, with cortical break seen in at least one plane. Bone erosion will be scored using a semiquantitative method based on the rheumatoid arthritis MRI scoring system (RAMRIS) [REF]; each bone will be scored separately on a scale from 0 to 10, based on the proportion of eroded bone compared with the ‘assessed bone volume’, judged on all available images—0: no erosion; 1: 1–10% of bone eroded; 2: 11–20%, etc. For long bones and large tarsal bones, the ‘assessed bone volume’ goes from the articular surface (or its best estimated position if absent) to a depth of 1 cm. Bone erosion was assessed at 22 bones in each foot (44 bones/patient). These sites are selected to include all bones in the foot and ankle except for the great toe distal phalanx and the lesser toe phalanges. The following bones will be scored: distal and proximal portions of the first proximal phalanx, first to fifth metatarsal (MT) heads, first to fifth MT bases, lateral, middle and medial cuneiforms, navicular, cuboid, anterior process of calcaneus, proximal calcaneus, distal talus, proximal talus and distal tibia.

Bone erosion score form

		Erosion score (RAMRIS)	
CT scoring system	**Visit**	**Baseline**	**Year 1**
	Date of scan		
Right	MTP1 head		
Right	MTP2 base		
Right	MTP3 base		
Right	MTP4 base		
Right	Cuneiform middle		
Right	Cuboid		
Right	Distal tibia		

Left	MTP1 head		
Left	MTP2 base		
Left	MTP3 base		
Left	MTP4 base		
Left	Cuneiform middle		
Left	Cuboid		
Left	Distal tibia		

RAMRIS scoring

Bone erosions: each bone is scored separately. The scale is 0–10, based on the proportion of eroded bone compared to the "assessed bone volume", judged on all available images—0: no erosion; 1: 1–10% of bone eroded; 2; 11–20%, etc. For long bones, the "assessed bone volume" is from the articular surface (or its best estimated position if absent) to a depth of 1 cm, and in tarsal bones (cuneiform and cuboid) it is the whole bone in the foot

In addition, erosion scoring will be done in additional bones (not part of study primary outcome)

Additional bones with erosion			
		Erosion score (RAMRIS)	
	Visit	**Baseline**	**Year 1**
	Date of scan		
Right			
Right			
Right			
Right			
Right			
Right			
Right			
Left			
Left			
Left			
Left			
Left			
Left			
Left			

10 Informed Consent (IC) Procedures

The process of IC will be carried out by one of the study investigators in conjunction with the study coordinator/research assistant involved in the screening visit after the participant appears to meet the pre-screening criteria. During the screening visit, the ICF will be read by the study participant and then each section will be explained by the research study coordinator obtaining consent. The participant will be given as

much time as they need to read and ask questions about the ICF. The individual or patient's legally authorized representative will be informed that he/she is not obligated to participate in the study and that it is strictly voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician. The IC process will ensure that there is no penalty for not participating in a clinical trial and that treatment will not be compromised if individuals do not participate, or if they cease participation at any time.

By signing the consent form, the participant authorizes the use of their personal health information (PHI), that they understand the study and its benefits and risks, and agree to all other aspects of the study outlined in the form. It allows the participant the opportunity to decide whether they want to participate in a study. During this process, individuals will be informed of all aspects of the study so that they can make an informed decision. Participants will then confirm their willingness to participate in the research study by signing the ICF.

After the participant has signed the consent form, the Principal Investigator (PI), and the research assistant conducting the visit will each sign and date the ICF. A signed version of the consent form will be kept by the study staff in the study binder and an additional copy of the consent form will also be given to the participant to keep.

The ICF contains the following:

- Disclosure of relevant information to prospective participants about the research
- The participant's comprehension of the information
- The participant's voluntary agreement to participate in a research study without coercion or undue influence
- Complete disclosure of any appropriate alternative procedures and their risks and benefits
- Disclosure of the extent of confidentiality that will be maintained
- Statement of compensation and/or medical treatment available if injury occurs
- Name, address, and telephone number of the PIs

If there is a change in any of the study procedures that may affect the participant, the ICF will be revised and approved by the Institutional Review Board (IRB). Any participants enrolled in the study prior to a change in procedures will sign the amended consent form. Signed consent forms will be kept as part of the study record for at least 7 years after completion of the study. Participants can withdraw their consent at any time by informing the study coordinator.

11 Study Medications

11.1 Denosumab

Denosumab (Prolia®) is a fully human monoclonal antibody with a high affinity (Kd 3 x 10(-12)M) for RANKL that can bind and neutralize the activity of human RANKL, similar to the action of endogenous OPG. The 3-year data from the randomized, double-blind, placebo controlled, phase III trial demonstrated that denosumab treatment reduced the incidence of new vertebral fractures, non-vertebral fractures and hip fractures when compared with placebo.[11] In the United States and Canada, denosumab has approvals for indications including the treatment of osteoporosis (OP) in postmenopausal women and men at high risk for fracture. In the European Union, denosumab has been approved for the treatment of OP in postmenopausal women at increased risk of fracture.

11.1.1 Packaging and Labeling of Clinical Supplies

Denosumab will be manufactured by Amgen Inc. Labeling and dispensation of study drug will be handled by the investigational pharmacies at UAB and University of Auckland. Study drug labeling will be annotated with the approved IRB protocol number(s).

11.1.2 Storage and return of Clinical Supplies

Investigational clinical supplies will be handled and stored safely and properly, and kept in a secured location to which only the PI and designated staff members have access. Clinical supplies will be dispensed only in accordance with the protocol. Study sites will keep accurate records of the clinical supplies received from Amgen, the amount dispensed for each patient, and the amount remaining at the conclusion of the study. The coordinator will mark the label of any vials that are not to be used with a large X, and document the reason for rejecting them on the drug accountability log. In accordance with good pharmacy practice, gloves will be worn during preparation of the dose. We will maintain an inventory of drug supplies received and dispensed. Upon completion or termination of the study, all unused denosumab will be returned to Amgen in the original container or authorized designate. All drug supply returns will be made to the study drug packaging and shipment vendor specified in the list of external facilities and personnel.

11.1.3 Denosumab Preparation and Administration

Denosumab will be presented as a pre-filled syringe (PFS) of 60 mg. All subjects will receive denosumab through a SC route of administration. Denosumab will not be administered intravenously, intramuscularly, or intradermal. All SC injections will be administered by authorized site personnel. Denosumab SC injection will be administered as the last procedure after all other study visit procedures have been completed. Prior to administration of denosumab it will be brought to room temperature in original container (allowed to stand ~15 to 30 minutes); it will not be warmed by any other method. The denosumab solution may contain trace amounts of translucent to white protein particles; however, it will not be used if cloudy, discolored (normal solution should be clear and colorless to pale yellow), or contains excessive particles or foreign matter. The study staff will avoid vigorous shaking. The study staff will administer via SC injection in the upper arm, upper thigh, or abdomen. The injection will not be administered in the same arm from which blood is drawn.

11.2 Urate Lowering Therapy (ULT)

All participants will continue with their ULT (e.g. allopurinol, febuxostat, probenecid, or combination ULT, except pegloticase) at the dosage, which was efficacious to maintain a sUA ≤5 mg/dL (300 µmol/L).

11.3 Concomitant Medications

Concomitant medications are defined as drug or biological products other than the study drug(s) taken by a participant during the clinical trial. This includes other prescription medications (including preventive vaccines), over-the-counter medications, herbal medications, vitamins, and food supplements. A comprehensive list of participant's concomitant medications will be collected at baseline and at each visit. This will include the name of the drug/vitamin/supplement, dose, route of administration, start and stop dates, and the reason for which the medication was taken. All medications will be listed by participant using the generic name(s) of the drug/vitamin/supplement. AE related to the use of a concomitant drug/vitamin/supplement will be documented on the adverse event case report form (CRF). Examples of all electronic forms can be found in Manual of Operating Procedures; Appendices 1

Medications that will not be allowed during participation in this study include the following:

- Alendronte (Fosamax®, Binosto®)
- Risedronate (Actonel®, Atelvia®)
- Ibandronate (Boniva®)
- Zoledronic Acid (Zometa®, Reclast®)

- Pamidronate (Aredia®)
- Teriparatide (Forteo®)
- Raloxifene (Evista®)f
- Pegloticase (Krystexxa®) within the past 6 monhs

11.4 Gout Flare Prophylaxis
Gout flare prophylaxis will be left to participant's doctor or provider in charge of managing gout..

11.5 Gout Flare Treatment
Gout flare treatment will be left to participant's doctor or provider in charge of managing gout.

12 Adverse Events (AE)
Definitions below incorporate guidelines provided by the Office of Human Research Protections (OHRP) of the Department of Health and Human Services (DHHS) and describes Food and Drug Administration (FDA) reporting requirements.

All AEs will be collected. An AE is any untoward event whether or not considered related to the use of denosumab or ULT. Any worsening (i.e. any clinically significant adverse change in frequency or intensity) of a preexisting condition which is temporally associated with the use of denosumab or ULT is also considered an AE. Abnormal laboratory values or test results constitute AEs only if they induce clinical signs or symptoms or require therapy, and are recorded on the AE CRF under the signs, symptoms or diagnosis associated with them. Screening conditions will not be considered adverse events; however, worsening of a preexisting condition may be considered an AE. We will report all AEs according to, the IRB, Amgen, Inc (per terms of the Safety Data Exchange Agreement), and the appropriate health authority (e.g., Food and Drug Administration [FDA]).

12.1 Serious AE (SAE)
Any AE occurring at any dose that results in any of the following outcomes:

- Death
- Is life-threatening (places the patient, in the view of the Investigator, at immediate risk of death from the AE as it occurred)
- Inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay, even if hospitalized as a precautionary measure for continued observation)
- A permanent, persistent, or significant disability (substantial disruption of the ability to conduct normal life functions). A medically significant AE that may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition
- Congenital anomaly/birth defect
- Other medically important serious event

Other events not considered to be SAEs:

- Hospitalization for treatment, which was elective or pre-planned, for a pre-existing condition that did not worsen
- Treatment on an emergency, outpatient basis for an event not fulfilling any of the definitions of serious given above and not resulting in hospital admission

12.2 Suspected Unexpected Serious Adverse Reaction (SUSARs).

Any adverse drug experience, the specificity or severity of which is not consistent with the current Investigator's Brochure.

12.3 AE Severity

The assessment of severity will be determined by the investigator and recorded on the electronic case report form (eCRF) for AE and SAE according to the investigator's best clinical judgment, taking into consideration various factors such as the subject's report, the physician's observations, and the physician's prior experience. The investigator will assess the individual AE severity using the following scale as defined by Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.[12]

12.3.1 Mild AE

Awareness of signs or symptoms, but easily tolerated and are of minor irritant type causing no loss of time from normal activities. Symptoms do not require therapy or a medical evaluation; signs and symptoms are transient

12.3.2 Moderate AE

Events introduce a low level of inconvenience or concern to the participant and may interfere with daily activities, but are usually improved by simple therapeutic measures; moderate experiences may cause some interference with functioning

12.3.3 Severe AE

Events interrupt the participant's normal daily activities and generally require systemic drug therapy or other treatment; they are usually incapacitating

12.4 Adverse Event (AE) Classifications

12.4.1 Expected AE

The Expected adverse effects of Denosumab could be found in the drug Investigator's Brochure. We are collecting adverse events at every visit.

12.4.2 Unexpected AE

Any AE, the specificity, frequency, or severity of which is not consistent with either:

The known or foreseeable risk of AEs associated with the procedures involved in the research that are described in the protocol-related documents, such as the IRB-approved research protocol, any applicable investigator brochure, the current IRB-approved informed consent document, and other relevant sources of information, such as product labeling and package inserts; or the expected natural progression of any underlying disease or condition of the participant(s) experiencing the AE.

12.4.2.1 Related to the research

An event is related to the research if, in the opinion of the investigators, it was more likely than not to be the result of the interventions and interactions used in the research or the collection of identifiable private information in the research (i.e., there is a reasonable possibility that the event may have been caused by participation in the research).

12.4.2.2 Unrelated to the research

An AE is unrelated to the research if, in the opinion of the investigators, the AE is not related to the research

12.4.3 Unanticipated problems involving risks to participants or others (unanticipated problems)

Problems that are (1) unexpected (in terms of nature, severity or frequency) given the research procedures and the participant population being studied; and (2) suggest that the research places participants or others at a greater risk of harm or discomfort related to the research than was previously known or recognized including physical, psychological, economic or social harm.

12.5 Relationship to study drugs

The determination of the likelihood that the study drug caused the AE will be provided by the study site Investigator. The study site Investigator's signature and date on the source document and eCRF that supports the causality noted on the AE form, ensures that a medically qualified assessment of causality was done. The assessment of relationship will be reported to the IRB and to the study sponsor (Amgen, Inc per safety data exchange agreement) by the study site Investigator according to his/her best clinical judgment. The following scale of criteria may be used as a guidance (not all criteria must be present in order to be indicative of a drug relationship).

12.5.1 Probably related to study drug

- There is evidence of exposure to the study drug
- The temporal sequence of the AE onset relative to administration of the study drug is reasonable
- The AE is more likely explained by the study drug than by another cause

12.5.2 Possibly related to study drug

- There is evidence of exposure to study drug
- The temporal sequence of the AE onset relative to administration of the study drug is reasonable
- The AE could have been due to another equally likely cause

12.5.3 Unlikely related to study drug

- There is evidence of exposure to the study drug
- There is another more likely cause of the AE
- There is no temporal relationship to study drug

12. Data management

13 Statistical Analyses

We intend to use the results of this pilot study to demonstrate feasibility, preliminary efficacy, and estimate potential effect sizes (with its accompanying 95% CI) that will lead to future grant submissions using other funding mechanisms. The primary outcome will be a change in the foot CT bone erosion score from baseline. Mean CT erosion scores at baseline among subjects enrolled in a previous study with zolendronic acid was 17.7 (SD 11.8)[3]. By enrolling 20 subjects to be randomized 1:1 we will have 80% power to detect a 16-point difference in the erosion score in favor of denosumab with a 5% significance level. However, it was agreed that if we can detect a 4-point erosion score difference over a year in favor of the Denosumab arm it will be considered clinically meaningful and will be considered a success for a pilot study, leading to consideration to proceed into a larger randomized clinical trial. Due to the positive correlation between the baseline and follow-up the variance of the change will be smaller in the follow-up than the baseline, thus our power should be higher than calculated. Parameters will be analyzed under an intention to treat basis. All dependent variables will be analyzed for normality or rendered and transformed if needed. Treatment and usual care will be compared by an analysis of covariance (ANCOVA) to test the difference in the change in each of the

parameters (CT Erosion, quality of life (QOL) indexes, pain scores, bone turnover marker scores) between groups, with baseline levels included as covariate. If normality assumption is violated, some transformation (such as log-transformation) will be applied. Least squares adjusted means, 95% confidence intervals, and standard error of the means will be presented. For AE indicators Fisher's exact test will be used to test for differences in numbers of participants who experienced at least one event or to compare categorical variables at baseline. Given the anticipated very small number of AEs, formal tests of statistical significance may not prove meaningful and will be significantly underpowered. We plan to use statistical inference through mean cumulative function on adverse event incidence. Student t test will be used to compare treatment groups at baseline

14 Safety Officer

As the safety of the study participants is the highest priority for this project we will appoint an independent safety officer, without conflict of interest with the study, to be responsible for evaluating the scientific issues related to the study. The Safety Officer will receive data periodically (e.g. every 12 months) including any pre-specified time points. The outcome of each patient is the top priority and as such, a process for the ongoing monitoring of results by independent scientists is important to maintain throughout the duration of the project.

Responsibilities

The Safety Officer responsibilities are to:

- Review the research protocol, ICFs and plans for data safety and monitoring
- Evaluate the progress of the trial, including periodic assessments of data quality and timeliness, recruitment, accrual and retention, participant risk versus benefit, and other factors that can affect study outcome
- Consider factors external to the study when relevant information becomes available, such as scientific or therapeutic developments that may have an impact on the safety of the participants or the ethics of the trial
- Review study performance, make recommendations and assist in the resolution of problems reported by the PI
- Protect the safety of the study participants
- Report on the safety and progress of the trial
- Make recommendations to the PIs, and, if required, to the FDA concerning continuation, termination or other modifications of the trial based on the observed beneficial or AEs of the treatment under study;
- Ensure the confidentiality of the study data and the results of monitoring
- Assist in the commenting on any problems with study conduct, enrollment, sample size and/or data collection
- The Safety Officer will discharge himself/herself from his/her duties when the last participant completes the study

14.2 Review Process

At the first meeting the Safety Officer will discuss the protocol, suggest modifications, and establish study monitoring guidelines. The Safety Officer, in consultation with the study team, will prepare the agenda to address the review of study materials, modifications to the study protocol and ICF, initiation of the trial, reporting of AEs, statistical analysis plan etc.

Meetings with the Safety Officer will be held twice a year. The study investigators and staff will attend most meetings. An emergency meeting may be called at any time by the Safety Officer or by the PI should participant safety questions or other unanticipated problems arise.

Meetings are closed to the public because discussions may address confidential participant data. Meetings may be convened as conference calls as well as in-person.

14.3 Meeting Format

Meetings will consist of open sessions. Discussion held in all sessions will be confidential. The PI and key members of the study team attend the open sessions. Discussion will focus on the conduct and progress of the study, including participant accrual, protocol compliance, and problems encountered.

Each meeting must include a recommendation to continue or to terminate the study and whether the Safety Officer has any concerns about participant safety. A recommendation to terminate the study may be made by the Safety Officer at any time. The Safety Officer will provide such a recommendation to the PI immediately by telephone and email.

14.4 Meeting Materials

Report templates will be prepared by the study staff, typically the statistician, to be reviewed by the Safety Officer at the first meeting. Format and content of the reports will be finalized and approved at the initial Safety Officer meeting, although changes throughout the trial may be requested. The reports will list and summarize safety data and describe the status of the study. All meeting materials will be sent to PI who will forward the materials to the Safety Officer at least 7 to 14 days prior to the meeting.

14.5 Reports

Reports generally include administrative reports by site that describe participants screened, enrolled, completed, and discontinued, as well as baseline characteristics of the study population. Other general information on study status may also be presented. Listings of AEs and SAEs as well as any other information requested by the Safety Officer may also be in the open session. The Safety Officer may direct additions and other modifications to the reports on a one-time or continuing basis. The reports may also contain data on study outcomes, including safety data, and perhaps efficacy data.

A formal report containing the recommendations for continuation or modifications of the study will be prepared by the Safety Officer. It is the responsibility of the PIs to distribute the Safety Officer recommendation to all co-investigators and to ensure that copies are submitted to the UAB and University of Auckland’s ethics committees.

14.6 Confidentiality

All materials, discussions, and proceedings of the Safety Officer are completely confidential. Members and other participants in SO? Meetings are expected to maintain confidentiality.

15 Investigational Study Sites

- University of Alabama at Birmingham, United States
- University of Auckland, New Zealand

Approximately 10 participants will be enrolled from each study site.

15.1 Site Recruitment

Investigational study sites will be two large academic medical centers. The study site staff will ensure participants are consented and randomized in accordance with established good clinical research practices. Additionally, site investigators and their staff will be required to have prerequisite human subjects training, and will answer study related questions, as needed.

15.2 Participant Recruitment and Consent

The site study staff will:

- Provide participants with adequate information concerning the study procedures, and scope
- Provide adequate opportunity for the participant to consider all available options
- Respond to the participant's questions and concerns
- Ensure that each participant understands all information provided
- Confirm that birth control is being used
- Obtain the participant's written voluntary consent to participate
- Sign the consent form as witnesses
- Provide participants with a copy of the consent form
- Keep the signed form in the participant's binder
- Attempt to schedule an early end of study assessment in the case of study drug discontinuation

15.3 Site Monitoring

Since this is a two site study, sites will be monitored by the PIs at each respective site (UAB or the University of Auckland) according to established monitoring standard operating procedures (SOPs). Study site PIs will oversee the study to assure satisfactory data recording, adherence to the study protocol, Good Clinical Practice (GCP), and study medication accounting. UAB and the University of Auckland will monitor recruitment utilizing automated reports generated from the study database. UAB and University of Auckland investigators and staff will have meetings monthly to monitor site recruitment and to determine any intervention for poor recruitment. The staff listed in the study roster will be responsible for all aspects of the trial. This includes but is not limited to the following:

- Development of the study protocol
- Development of the manual of procedures and its maintenance
- Participant randomization
- Development and implementation of the data flow and data tracking
- Development of procedures for data entry, error identification, and error correction
- AE monitoring and reporting
- Quality control procedures
- Submitting for IRB review and approval
- Creating reports - enrollment, AEs, participant status (e.g., withdrawals)
- Preparing and sending required reports to the Safety Officer and the IRB
- Submitting all required reports to the study appointed Safety Officer.
- Distribution of all changes, updates and policies of above mentioned reports and documents to the study appointed Safety Officer.
- Maintaining the study binder (regulatory and clinical documents)
- Preparation of all study materials- data tables, recruitment materials, official reports
- Identifying, recruiting, screening, and enrolling participants
- Obtaining IC from each participant
- Protecting participants' rights
- Collecting study data and following participants through study completion
- Compliance and accountability of administration of study intervention
- Communicating questions, concerns, and/or observations to the PIs

All of the above activities will be carried out by the study's project coordinators, project managers, and research assistants on a weekly basis (or more frequently as needed) and monitored by the principal and co-investigators.

In the event a problem is identified by either study site PI or staff, a teleconference/webinar will be scheduled to review the issue. These teleconferences/webinars will include discussions of overall recruitment status and identified barriers to recruitment experienced by the site with the study team. Detailed recruitment issues and suggestions will be discussed, as well as identified barriers.

The study will be conducted under the auspices of the IRBs at UAB and the University of Auckland. The respective site investigators will ensure that an appropriately constituted IRB that complies with the requirements of the current International Conference on Harmonization (ICH)-GCP version or applicable regulations will be responsible for the initial and continuing review and approval of the clinical study. Prior to initiation of the study, the investigator will forward copies of the protocol, ICF, Investigator's Brochure, Investigator's curriculum vitae (if applicable), study advertisements (if applicable), and all other subject-related documents to be used for the study to the IRB for its review and approval. Before initiating a study, the site PI will have written and dated full approval from the responsible IRB for the protocol. The investigators will also promptly report to the IRB all changes in the study, all unanticipated problems involving risks to human subjects or others, and any protocol deviations, to eliminate immediate hazards to subjects.

16 Institutional Review Board (IRB)

The study site PI and/or staff will not make any changes in the study or study conduct without IRB approval, except where necessary to eliminate apparent immediate hazards to the subjects. For minor changes to a previously approved protocol during the period covered by the original approval, it may be possible for the study site PI to obtain an expedited review by the IRB as allowed. As part of the IRB requirements for continuing review of approved studies, the Investigators will be responsible for submitting periodic progress reports to the IRB (based on the Committee's requirements), at intervals appropriate to the degree of subject risk involved but no less than once per year. The study site PI should provide a final report to the IRB following study completion. To the maximal extent possible, these functions will be assisted by study personnel at the Coordinating Center (CC), the University of Alabama at Birmingham.

17 Administrative Procedures

17.1 Protocol Amendments

Any change that affects the conduct of the study or significantly alters the protocol will be made in the form of an amendment. Any change or addition to this protocol requires a written protocol amendment that must be approved by the CC before implementation. Amendments significantly affecting the safety of participants, the scope of the investigation, or the scientific quality of the study require additional approval by the IRB. Examples of amendments requiring such approval are:

- An increase in drug dosage or duration of participant exposure
- A significant change in the study design (e.g. addition of a new immunosuppressive)
- An increase in the number of study visits and procedures to which participants are exposed

17.2 Compliance with law, audit, and debarment

Study site PIs will conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of GCP; and all applicable federal, state, and local laws, rules and regulations

relating to the conduct of the clinical study. The study site PIs also agree to allow the Safety Officer, IRB/Independent Ethics Committee, and regulatory agencies to inspect and review trial-related documents and procedures, and provide for direct access to all study-related source data and documents. The study site PIs will not seek reimbursement from patients, their insurance providers, or from government programs for procedures included as part of the study.

The study site PIs will prepare and maintain complete and accurate study documentation in compliance with GCP standards and applicable federal, state, and local laws, rules and regulations.

Study documentation will be promptly and fully disclosed by the study site PI upon request for inspection, copying, review, and audit at reasonable times by any regulatory agencies. The study site PI agrees to promptly take any reasonable steps that are requested by designated representatives as a result of an audit to cure deficiencies in the study documentation and CRFs.

Persons debarred from conducting or working on clinical studies by any court or regulatory agency will NOT be allowed to conduct or work on this studies.

17.3 Compliance with Financial Disclosure Requirements

The study site PIs will provide accurate financial information to allow submission of complete and accurate certification and disclosure statements as required by US FDA regulations (21 CFR Part 54) and/or New Zealand. This requirement also extends to sub-Investigators.

17.4 Publication of results

It is mandatory that the first publication will be based on data from both centers that has been analyzed as stipulated in the protocol. Participating PIs agree not to present data gathered from one center before the full publication, unless formally agreed to by all other PIs.

17.5 Changes in study personnel

If there is a change of any personnel listed on the Form FDA 1572, a new form reflecting the change will be completed and forwarded to the IRB along with the new staff member’s signed curriculum vitae, medical license (if relevant), and signed financial disclosure statement.

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